Otsuka S, Maegawa S, Takamura A, Kamitani H, Watanabe T, Oshimura M, Nanba E	Aberrant promoter methylation and expression of the imprinted PEG3 gene in glioma	Proc Jpn Acad Ser B Phys Biol Sci	85	157-165	2009
Otomo T, Higaki K, Nanba E, Ozono K, Sakai N	Inhibition of autophagosome formation restores mitochondrial function in mucolipidosis II and III skin fibroblasts	Mol Genet Metab	98	393-399	2009
Osaki Y, Ben-Shlomo Y, Lees AJ, Wenning GK, Quinn NP	A validation exercise on the new diagnostic criteria for multiple system atrophy	Mov Disord	24	2272-2276	2009
Osaki Y, Morita Y, Fukumoto M, Akagi N, Yoshida S, Doi Y	Cross sectional and longitudinal studies of three-dimensional stereotactic surface projection SPECT analysis in Parkinson's disease with and without dementia	Mov Disord	24	1475-1480	2009

IV. 研究成果の刊行物・別冊

運動ニューロン疾患

運動ニューロン疾患の分類と疫学

■分類

運動ニューロンには中心前回のBetz(ベッツ)巨細胞に代表される上位運動ニューロン(UMN；一次運動ニューロン)と脳幹運動神経核・脊髄前角に存在する下位運動ニューロン(LMN；二次運動ニューロン)とがある(図9-90)．運動ニューロン疾患とは，この運動ニューロンが優位におかされて臨床的に運動ニューロン症候(表9-58)が主病像を形成する疾患群を指す．

UMNとLMNの両者がおかされる場合は筋萎縮性側索硬化症(ALS)と呼ばれ，UMNのみが選択的におかされると原発性側索硬化症，LMNのみがおかされると脊髄性筋萎縮症と呼ばれる．

運動ニューロンの障害部位による分類のほかに，孤発性か遺伝性かという観点から分類することもある．

■疫学

ALSの発生率は一般に10万人あたり1～2人といわれ，このうち5～15%が家族性と考えられている．家族性ALSのうち，約2割が後述の変異SOD1(superoxide dismutase 1)を有する遺伝性ALSである．

〔中野今治〕

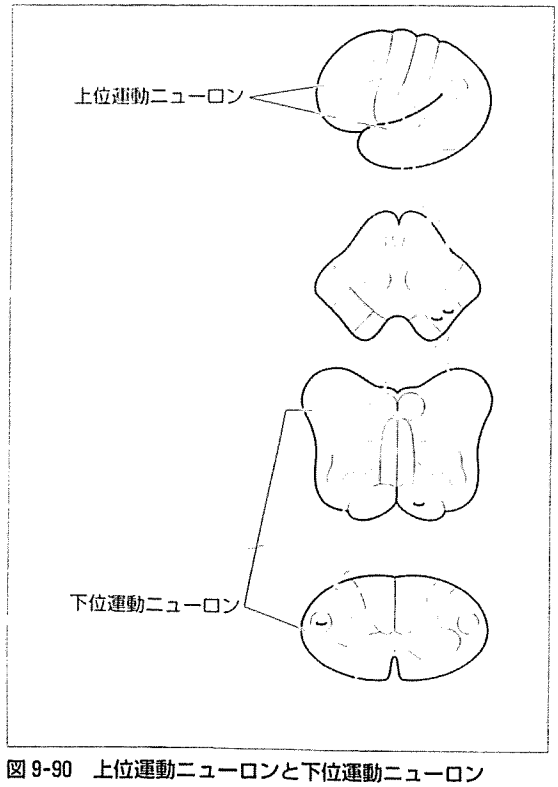


図9-90 上位運動ニューロンと下位運動ニューロン

1 筋萎縮性側索硬化症，家族性筋萎縮性側索硬化症

筋萎縮性側索硬化症(ALS)には孤発性ALSと家族性ALSとがある．前者の代表が古典型〔Charcot(シャルコー)病〕といわれて，孤発性に発症するタイプである．本項ではALSといえば，この古典型を指すことにする．それに対して，家族性ALSは家族発症するタイプであり，その大多数は遺伝性と考えられている．

筋萎縮性側索硬化症
amyotrophic lateral sclerosis(ALS)

■概念

UMNとLMNが選択的進行性におかされ，数年で呼吸不全を呈して死亡する運動ニューロン疾患である．

表9-58 神経変性疾患における運動ニューロン症候

症候	障害部位	
	上位運動ニューロン	下位運動ニューロン
筋力低下	軽度	高度
筋萎縮	なし	高度
線維束性収縮	なし	出現
腱反射	亢進	低下～消失
筋緊張	亢進(痙縮，クローヌス)	低下(筋弛緩)
Babinski徴候，Chaddock徴候	陽性	陰性
手指の巧緻運動	軽度障害	高度障害

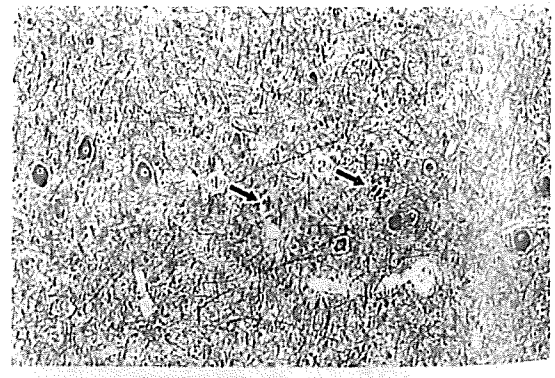


図9-91 筋萎縮性側索硬化症のBétz巨細胞
本例ではよく保存されているようにみえるが，一部は変性(矢印①)，あるいは消失(矢印②)しており，後者では掃きたマクロファージが認められる．(KB染色，×100)

■病理・病態生理

ALSの基本的病理は，中心前回のBetz巨細胞に代表される大型ニューロン(図9-91)の脱落，および脳神経運動核の一部(三叉神経運動核，顔面神経核，疑核，副神経核，舌下神経核)と脊髄前角の大型運動ニューロンの脱落である(図9-92)．中心前回ニューロンの脱落とともにその投射路(皮質核路と皮質脊髄路)が変性する．軸索が変性するとそれを取り巻いている髄鞘も崩壊して髄鞘染色〔Klüver-Barrera(KB)染色〕で染まらなくなるので，皮質脊髄路(錐体側索路と錐体前索路)は淡明に見える(図9-93)．

残存しているLMNでは，ほぼ正常に見えるニューロンからさまざまの程度の変性像を呈するニューロンまでが認められる．一部のLMNは好酸性(HE染色で赤く染まること)でしばしば数珠(じゅず)状に連なる円形封入体〔Bunina(ブニナ)小体〕を含んでいる(図9-94)．Bunina小体はALSでのみ出現する重要な構造物である．また，ALSの前角ニューロンにはユビキチン化した封入体(skein-like inclusionとround inclusion)が出現する．この構成成分がTDP-43であることが最近報告された．

運動ニューロン死の機序として酸化ストレス説，ウイルス説，自己免疫説，外毒素説，興奮性アミノ酸(グルタミン酸が代表的)過剰説などが挙げられているが，真の原因は不明である．ALSにおけるLMN死の機序として現在最も注目されているのが，グルタミン酸受容体の1つであるAMPA受容体の分子的変化である．内部に大量のCa^{2+}が流入するとその神経細胞は細胞死に陥る．AMPA受容体はこのCa^{2+}流入を調節しており，その調節に決定的役割を果たすのが受容体のサブユニットの1つであるGluR2である．ALS症例のLMNのGluR2では，元来アルギニンである部位がグルタミンになっており，そのためにCa^{2+}が流入して運動ニューロン死が起こると推測されている．

■臨床所見

◐初発症状

初発症状として最も多いのは，上肢遠位部の筋力低下と筋萎縮である．初期には通常左右のどちらかがおかされる．前腕筋がおかされると握力の低下として現れ，手内筋がおかされると箸がうまく使えない，字がうまく書けないなどの指の巧緻運動障害が出現する．

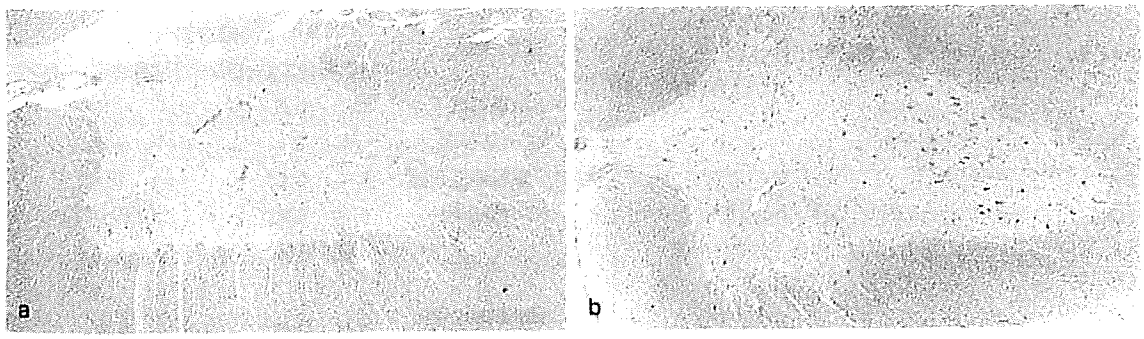


図9-92 筋萎縮性側索硬化症の頸髄前角(a)
対照(b)に比して大型のLMNが高度に脱落している．(KB染色，×40)

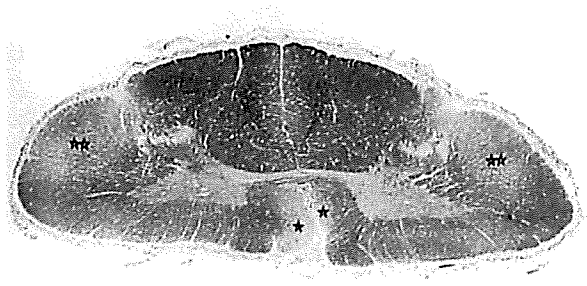


図9-93 筋萎縮性側索硬化症の頸髄
錐体側索路(**)と錐体前索路(*)の淡明化がみられる．(KB染色)

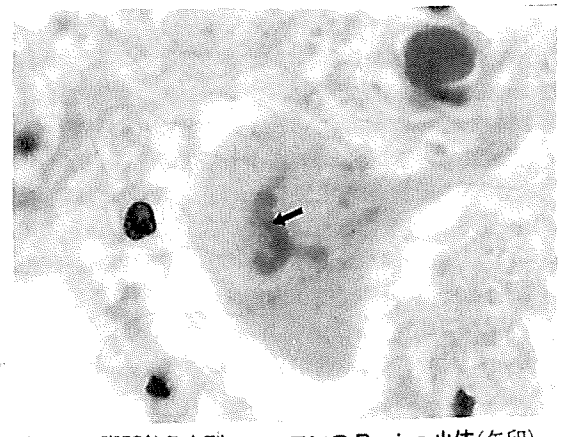


図9-94 脊髄前角大型ニューロンのBunina小体(矢印)
(HE染色，×400)

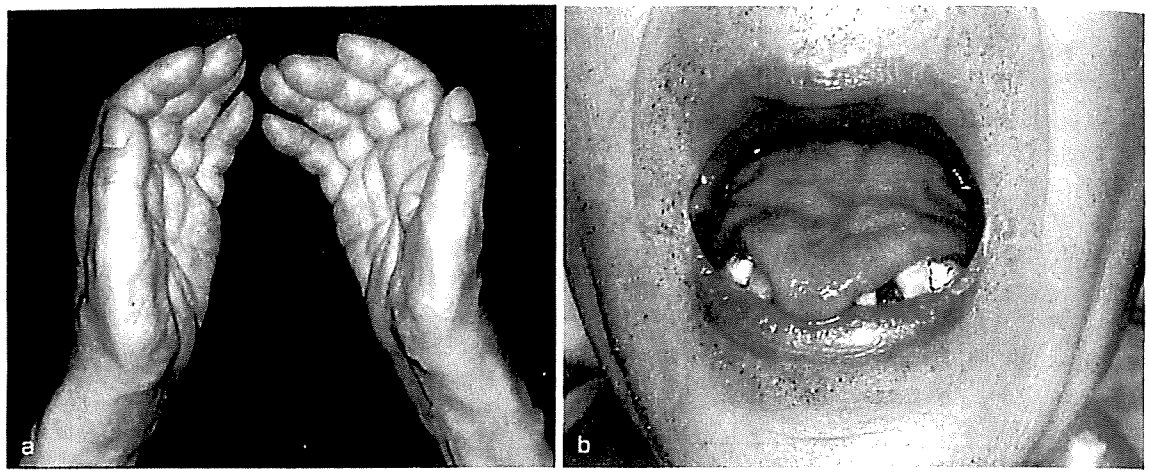


図 9-95 筋萎縮性側索硬化症の下位運動ニューロン障害による筋萎縮
母指球(a)と舌(b).

2番目に多い初発症状は球麻痺症状であり，なかでも舌筋の運動障害に伴う構音障害が多い．

②臨床像

麻痺 いずれの部位から初発しても，筋力低下と筋萎縮は他の部位に徐々に拡大して，球麻痺，四肢麻痺となり数年後には大多数の患者は臥床状態となる．後頸筋群がおかされると頸下がりの状態となり，このときには通常前頸筋群もおかされるので，仰臥位から起き上がるときに頭部を持ち上げられなくなる．

筋萎縮 おかされた筋には筋萎縮と線維束性収縮が認められる．手においては母指球(図 9-95a)と第1背側骨間筋の萎縮が最も同定しやすい．前脛骨筋が萎縮すると，その前縁は脛骨前縁よりも後退するので，前脛骨筋の萎縮も同定しやすい．舌は正常では多少隆起した滑らかな表面を有しているが，萎縮すると凹凸を示すようになる(図 9-95b)．

線維束性収縮 1個の前角運動ニューロンとそれが支配する筋線維群を運動単位といい，1運動単位に属する筋線維の数を神経支配比といい，おおよそ 100～数 100 である．線維束性収縮は，LMN の不随意な興奮によってその運動単位に属する筋線維がすべて同期して収縮する現象であり，数 100 の筋線維が同時に束として(筋線維束)として収縮することから，肉眼的に観察できる．これに対し，個々の筋線維がばらばらに収縮する線維性収縮は肉眼的には観察できない．線維束性収縮は三角筋や大胸筋などの上肢帯筋，母指球や背側骨間筋，大腿四頭筋の内側頭，オトガイ舌筋でよくみられる．

猿手・鷲手 母指球筋が高度に障害されると母指の対立ができなくなり，手で持つのに第2～5指のみと手掌を使うようになる(猿手；サルは元来母指の対立ができない)．また，中手指節間関節を屈曲し，指節間関節を伸展するのは手内筋である骨間筋と虫様筋である．この筋の筋力低下が生じると中手指節間関節が伸展し，指節間関節の屈曲した状態となる(鷲手)．

球麻痺 舌が萎縮して運動障害が高度になると，発話は遅く不明瞭になる．また，口腔内の食塊を滑らかに咽頭に送り込むことができなくなり，さらには咽頭筋の麻痺により反射性の嚥下運動が障害され，誤嚥をきたすようになる．

呼吸筋麻痺 ALS の進行期に入ると，横隔膜，肋間筋など呼吸筋がおかされ呼吸不全になる．横隔膜が優位におかされたときには，吸気相で腹部が陥凹する奇異性呼吸を示す．

陰性4徴候 ALS でみられない4つの徴候のことをいい，外眼筋麻痺，感覚障害，排尿(便)障害，褥瘡(じょくそう)を指す．

■検査所見

針筋電図検査 ALS の診断に最も重要な検査である．まず，消失した LMN で支配されていた筋線維群は神経支配を逃れて(脱神経支配)，個々に自発的に収縮するようになる(線維性収縮)．これの電気活動が線維自発電位 fibrillation potential である．ついで，残存した LMN の軸索末端からの発芽 sprouting により，一部の筋線維の再支配が生じるが，新たに形成された側枝の伝導時間は正常より長く，また新しいシナプスでの伝達も不安定であるので，多相性で持続の長い運動単位電位を示す．やがて，再支配が完成してシナプス伝達も安定してくると，1つの運動単位が支配する筋線維の数が増えるので，高振幅，長持続，多相性のいわゆる神経原性変化を示すようになる(図 9-96)．ALS では，それぞれの運動単位が異なった変性過程にあるので，針筋電図でも脱神経電位(線維自発電位)から高振幅まで種々の運動単位電位を示す．

神経伝導検査 伝導速度の遅延や伝導ブロックはないが，複合筋活動電位の低下がみられる．

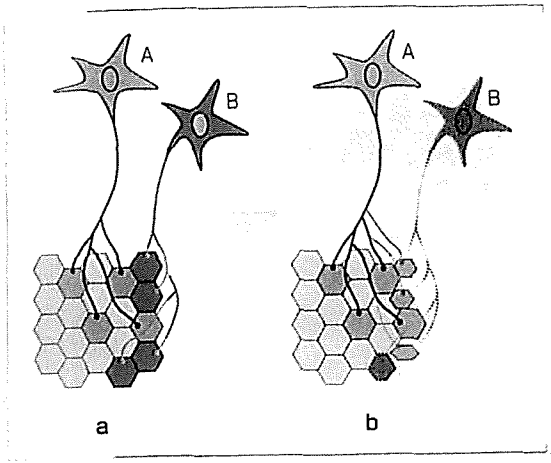


図 9-96 筋萎縮性側索硬化症の針筋電図
下位運動ニューロン A，B が初めはそれぞれ 4 本の筋線維を支配している(a)が，B が死ぬとそれに支配されていた筋線維はほかの残存ニューロンからの発芽線維(赤)で支配されるようになる(b)．ただし，いったん脱神経状態になった筋線維は，再支配の完了までに種々の程度に萎縮すると思われる．ここでは A から 3 本の軸索が伸びているが，その支配筋線維数は 4 本から 7 本に増えている．このような状況では A が興奮したときの電位は振幅が高くなり，7 本の筋線維すべてに刺激が伝わるのもばらつくので，多巣性，長期持続型となる．

血液生化学的検査　CK 値が軽度から中等度上昇しているのが認められることがまれでない．

脳脊髄液検査　細胞増多はないが，総蛋白の上昇がみられることがある．

■診断

ALS の診断は，UMN 障害と LMN 障害の症候の存在(表 9-58)，陰性 4 徴候の存在，進行性の経過，および針筋電図の神経原性変化から診断する．ただし，UMN 症候がみられない例はまれでなく，Babinski(バビンスキー)徴候や Chaddock(チャドック)徴候がみられる頻度は高くない．

■鑑別診断

変形性頸椎症　頸椎症で感覚障害を伴わずに上肢の筋萎縮と筋力低下，および下肢の UMN 症候を呈する場合があり，ALS との鑑別に迷うことが少なくない．頸椎症では球症状や下肢の LMN 症候がみられないこと，および頸筋の筋力低下がみられないことから鑑別する．

球脊髄性筋萎縮症　四肢と球部の筋萎縮と筋力低下を示し，感覚障害がみられないことから ALS と誤診されることがある．球脊髄性筋萎縮症は，女性化乳房，姿勢・動作時振戦，発話時の顔面筋のびくつきなどから鑑別できる．診断確定にはアンドロゲン受容体遺伝子の CAG リピート伸張を証明する．

多巣性運動ニューロパチー　上肢主体に緩徐進行性の筋萎縮と筋力低下をきたし，線維束性収縮が出現し，腱反射が保たれることもある脱髄性疾患である．神経伝導検査で伝導ブロックが証明されることから ALS と鑑別できる．

家族性 ALS　特に後述する SOD 1 変異を有する家族性 ALS(SOD1-FALS)では孤発性発症があるので，30～40 歳代発症で 1 年以内に呼吸不全に陥るような症例では SOD1-FALS を鑑別する必要がある．

糖尿病性筋萎縮　糖尿病患者は，特に下肢近位部に急速な筋萎縮と筋力低下を呈することがある．この場合は，通常障害部位の痛みを伴うことから鑑別できる．

若年性一側上肢筋萎縮症(平山病)　若年男子の一側上肢遠位部尺側主体に筋萎縮と筋力低下を呈する疾患である．特徴的な筋萎縮分布と進行の停止，頸部前屈時に頸髄が前方に移動する画像所見から診断できる．

脊髄空洞症　筋萎縮と筋力低下が初期には一側の手に現れ，前腕へと進む．運動症候のみの場合があるので，ALS との鑑別を要する．頸椎 MRI で診断可能である．

■経過・予後

ALS 症状は常時進行性である．球部，上肢，下肢いずれの部位から初発しても筋萎縮と筋力低下は全身に及んで最終的には寝たきりとなる．死因の多くは，拘束性呼吸不全を背景にして併発する肺炎や球麻痺に伴う嚥下性肺炎である．罹病期間は大多数の患者では 3～5 年であるが，まれには 1 年と短い例や，10～20 年の長期例もある．

■治療

根治療法はない．抗グルタミン酸作用を示すリルゾールが承認されている唯一の薬物である．

筋力低下，嚥下障害，呼吸不全に対する対症的な療法が ALS 治療の主体である．

① 家族性筋萎縮性側索硬化症
familial amyotrophic lateral sclerosis(FALS)

■概念

家族性に発症する ALS のことであり，雑多な原因によるものが含まれるが，多くは遺伝性である．筋萎縮性側索硬化症の 5～10% は家族性 ALS である．1993 年，後索や脊髄小脳路がおかされる後索型家族性 ALS において，第 21 染色体に位置する SOD1(superoxide dismutase 1)遺伝子の変異が見いだされた(SOD1-FALS)．

現在，遺伝子あるいは遺伝子座が判明した家族性 ALS には番号が付けられ，ALS1～8 がある．SOD1-FALS は ALS1 と命名され，家族性 ALS のうち約 20% を占め，常染色体性優性遺伝形式を呈する．SOD1 の遺伝子変異は現在 100 以上報告されており，大多数は点変異である．

SOD1-FALS 以外の家族性 ALS はごくまれである

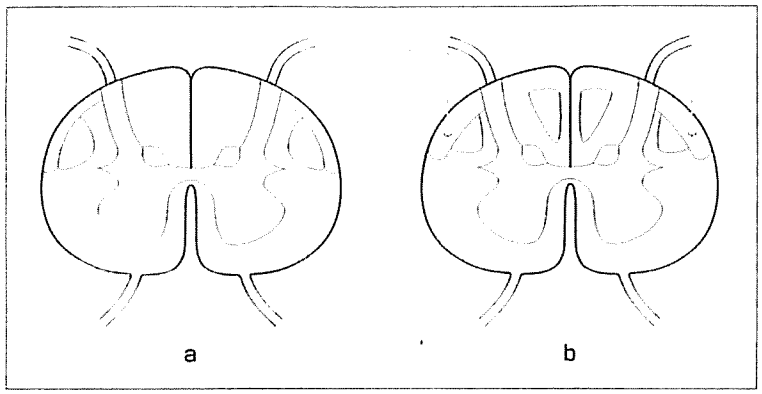


図 9-97 古典型筋萎縮性側索硬化症(a)とSOD1-FALS(b)の脊髄病変の模式図
SOD1-FALSにおいてはALS病変部位に加えて，Clarke柱，後脊髄小脳路および後索中間根帯に変性がみられる．

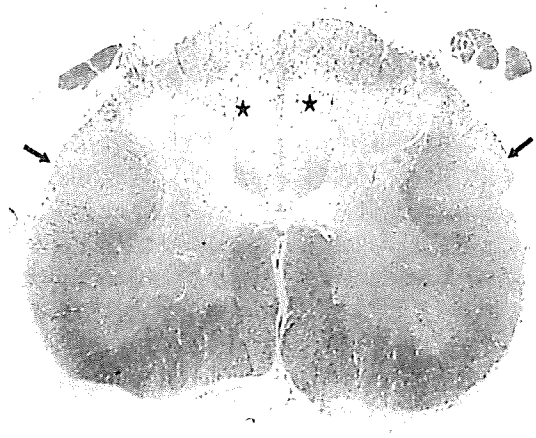


図 9-98 SOD1-FALSの腰髄
後索中間根帯(星印)と錐体側索路(矢印)の淡明化がみられる．(KB染色)

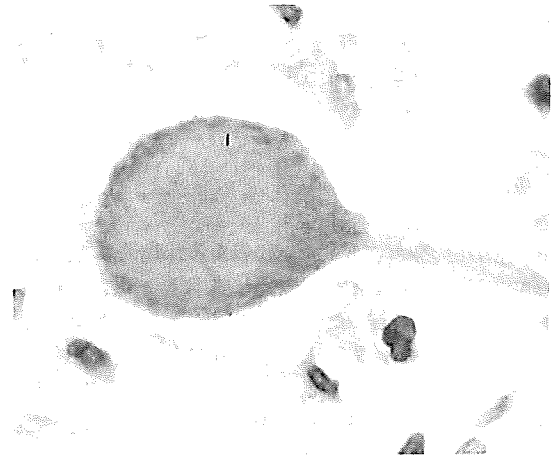


図 9-99 SOD1-FALSの前角細胞内のLewy body-like hyaline inclusion
(HE染色，×400)

ので，ここではSOD1-FALSについて述べる．

■病理・病態生理

SOD1-FALSの神経病理はSOD1遺伝子の変異部位によって差異がみられるが，半数を占めるとされるArg4Val(SOD1の4番目に位置するアルギニンがバリンに置換した)変異例では，UMNとLMNの変性に加えて，後索中間根帯，Clarke(クラーク)柱，後脊髄小脳路の変性が認められる(図9-97，98)．残存する運動ニューロンには抗ユビキチン抗体で陽性に染まるLewy body-like hyaline inclusion(レヴィ小体様硝子封入体)が観察される(図9-99)．また，LMNの軸索はしばしばコード様に腫大し，その一部は抗ユビキチン抗体で染色される．Bunina小体は認められず，ユビキチン陽性の封入体も形態や分布において古典型ALSとは異なっている．

SOD1は生体内で産生されたフリーラジカルを処理するのに重要な酵素であるが，このノックアウトマウスでは症状が出ないことから変異SOD 1が毒性作用を有するのではないか(gain of toxic function)と推測されている．

■臨床所見

孤発性ALSよりも若年発症が多いが，発症年齢は15～81歳と大きくばらつく．発症部位は四肢，体幹，あるいは球部である．一般にLMN症候が前景にたち，これにさまざまな程度のUMN症候が加わる．家系間での症候のばらつきに加えて，Asp90Ala変異のように同一家系においても症候の不均一性がみられる．

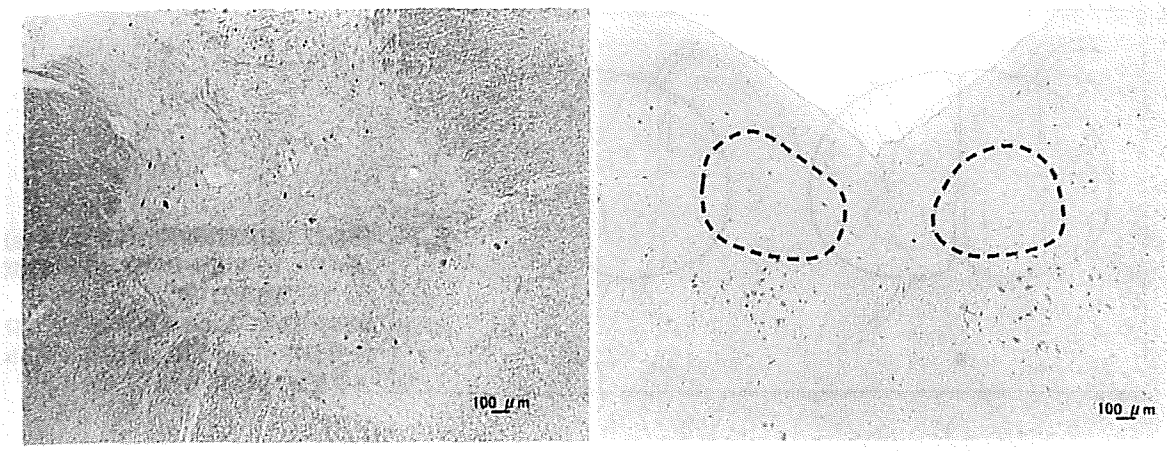
■検査所見

電気生理学的には，古典型ALSと同様である．SOD1遺伝子の変異がみられる．

■診断・鑑別診断

臨床像からは古典型ALSと区別できない．常染色体性優性遺伝形式を示す家族歴がある場合には，本症が強く考えられる．SOD1遺伝子変異を見いだせば診断は確定する．孤発性発症例があるので，30～40歳代発症で1年以内に呼吸不全に陥るような症例ではSOD1-FALSを除外する必要がある．

鑑別診断には，孤発性ALSの項で挙げたような疾



a　　b

図 9-100　球脊髄性筋萎縮症の腰髄前角(a)と舌下神経核(b，破線内)
いずれも大型運動ニューロンが高度に脱落している．舌下神経核腹側(b の下方)に見える細胞群は Roller 体．(KB 染色，×40)

患が挙がる．

■経過・予後

SOD1 の変異ごとに経過が大いに異なる．例えば，Arg4Val 変異家系では急速に進行してほぼ 1 年で死亡することが知られているのに対して，進行が緩徐で 10 年以上の経過を有する SOD1 変異も複数知られている．

〔中野今治〕

2 球脊髄性筋萎縮症〔Kennedy-Alter-Sung(ケネディ-アルター-ソン)病〕

bulbospinal muscular atrophy

■概念

X 染色体上のアンドロゲン受容体遺伝子の CAG リピートの異常伸長により生じる~~伴性劣性の~~下位運動ニューロン疾患である．(男性に)

■病理・病態生理

基本的な病理像は脊髄前角と脳神経運動核の LMN の脱落消失である(図 9-100)．UMN はおかされない．残存する LMN の核は抗ポリグルタミン抗体で均質に染色され，その一部は核内封入体を形成する．骨格筋でも同様の現象が認められる．

アンドロゲン受容体蛋白は細胞質内で合成され，テストステロンが結合すると核内に移行する．この受容体の遺伝子中の CAG(グルタミンをコードする)リピートが異常伸長するとアンドロゲン受容体蛋白は異常に伸長したポリグルタミン鎖をもつようになる．これにテストステロンが結合すると核内に移行して凝集し，この凝集体が核機能を障害して細胞死を引き起こすと考えられている．実際，異常伸長した CAG をもつアンドロゲン受容体を導入したマウスでは，テストステロンを大量に産生する雄のみが発症し，去勢すると症状が軽快する．逆に発症しない雌にテストステロンを投与すると発症する．ただし，運動ニューロンに限局して細胞死が生じる機序は解明されていない．

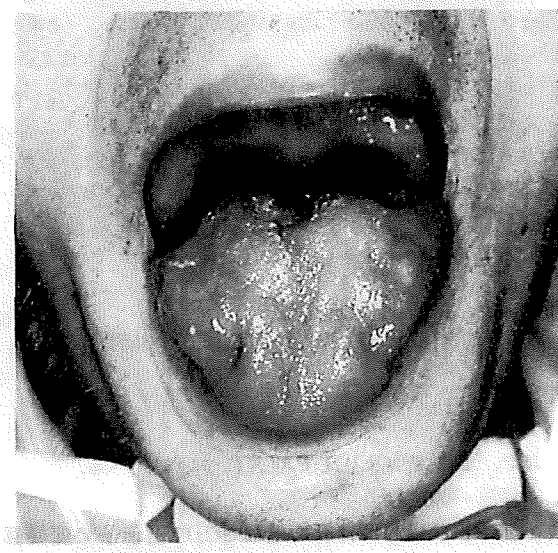


図 9-101　球脊髄性筋萎縮症の舌
高度の萎縮にもかかわらず挺舌は十分可能である．

■臨床所見

男性のみが罹患する．通常 40～60 歳で発症し，初発症状は易疲労性，筋けいれん，四肢筋力低下である．球麻痺症状(構音障害)で初発することもある．筋力低下は近位筋優位の分布を示すが，逆の場合もある．筋萎縮と線維束性収縮がみられる．軽度の等尺性収縮に伴って粗大な線維束性収縮様の収縮(収縮時線維束性収縮 contraction fasciculation)が観察される．これは特に口周囲筋で目立ち，発話などの際にこの部の不規

表 9-59 脊髄性筋萎縮症(SMA)の分類

タイプ	発症年齢(歳)	*SMN1* 変異率	運動機能	生命予後
SMA Ⅰ型(重症型)〔Werdnig-Hoffmann(ウェルドニッヒ-ホフマン)病〕	0～0.5	95% 以上	座位保持不能	2年未満
SMA Ⅱ型(中間型)	0.5～1.5	同上	座位可，立位保持不能	2年以上
SMA Ⅲ型(軽症型)〔Kugelberg-Welander(クーゲルベルク-ヴェランダー)病〕	>1.5	同上	独立立位保持可能	成人まで生存
SMA Ⅳ型(成人型)	成人	不明	下位運動ニューロン症候(発症前は正常機能)	長期

則な攣縮様の動きとして観察される．

球麻痺症状は構音障害が特徴で，軟口蓋麻痺に伴う開鼻声が認められる．進行すると咀嚼障害と嚥下障害が出現し，上気道炎に併発する声帯麻痺による窒息がみられる．この場合には緊急挿管，さらには気管切開が必要となる．

本症に特徴的な所見の1つは，舌の著明な萎縮とそれによる深い溝がみられる(図 9-101)ことだが，萎縮に不釣り合いに舌の動きがよい(挺舌は十分可能)のも特徴である．

下肢遠位部に軽度から中等度の感覚障害がみられることがある．

神経症候以外の所見としては，女性化乳房，精巣(睾丸)萎縮，インポテンスが認められる．

■検査所見

針筋電図では，活動運動単位の減少を認め，運動単位電位は振幅が大きく(giant spike)，多相性で持続が長い．干渉波は不十分となる．

血清 CK 値はほぼ全例で正常の数倍に達する．肝機能障害を反映して血清 AST と ALT の軽度の上昇がみられる．脳脊髄液では総蛋白が軽度に上昇することがある．

■診断

診断は，四肢の筋力低下，口周囲筋のびくつき，手指の姿勢時振戦，女性化乳房などから本症を疑うことに始まる．確定診断はアンドロゲン受容体遺伝子の CAG 伸長を証明することである．

■鑑別診断

筋萎縮性側索硬化症，家族性筋萎縮性側索硬化症，脊髄性筋萎縮症，重症筋無力症，肢帯型筋ジストロフィー，多発性筋炎などが主要な鑑別疾患である．特に筋萎縮性側索硬化症と誤診されることが多いので注意を要する．

■経過・予後

症状の進行はきわめて緩徐で，筋力低下の自覚から10数年は就労可能である．進行期の転倒や誤嚥など合併症対策をしっかり施せば生命予後は良好である．また，CAG リピート数が多いほど発症年齢が若くなる傾向がある．

■治療

前述したような本症の動物モデルでは，異常アンドロゲンの核内集簇を阻止することで治療できる．この所見に基づいて，現在リュープロレリンを用いた臨床治験が実施されており，その有効性が期待されている．

〔中野今治〕

3 脊髄性筋萎縮症
spinal muscular atrophy(SMA)

■概念

脊髄性筋萎縮症(SMA)は，脊髄の LMN と脳神経運動核の一部(Ⅴ，Ⅶ，Ⅹ，Ⅻ)の変性・脱落により筋力低下と筋萎縮を呈する，複数の原因で生じる疾患群である．発症年齢と重症度により4型に分類される(表 9-59)．SMA の多くは，第5染色体長腕(5q13)に位置する survival of motor neuron(SMN)遺伝子(*SMN*)に変異を有する常染色体性劣性遺伝性疾患である．

■病理・病態生理

本質は LMN の萎縮，消失であり，LMN のニッスル小体中心崩壊がみられる．封入体や炎症反応は認められない．錐体路はおかされない．SMA Ⅰ型では，生検筋で胎児期の筋肉の像がみられ，発達障害の可能性が推測されている．

SMN は塩基配列にほとんど差のみられない2つのコピー(テロメア側に位置する *SMN1* とセントロメア側に位置する *SMN2*)を含んでいる．*SMN1* の変異で発症が決定され，*SMN2* のコピー数でタイプが決まると考えられている．ただし，何故 LMN にのみ障害が生じるのかは解明されていない．

Original Paper

Neuro
epidemiology

Neuroepidemiology 2009;32:101–106
DOI: 10.1159/000177035

Received: June 21, 2008
Accepted: September 11, 2008
Published online: November 27, 2008

Prevalence of Dementia in the Rural Island Town of Ama-cho, Japan

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Key Words
Alzheimer's disease · Vascular dementia · Dementia with Lewy bodies · Parkinson's disease · Progressive supranuclear palsy · Frontotemporal lobar degeneration

Abstract
Background: With the striking increase in the number of elderly people in Japan, dementia has not only become a medical but also a social issue. ***Methods:*** We studied the prevalence of dementing disorders in a rural island town of Japan (Ama-cho), using a door-to-door 2-phase design. ***Results:*** Of the 120 persons screened as having cognitive impairment, 104 people were diagnosed as having dementia. The prevalence (cases/100 persons aged 65 years and older) was 11.0 for all types of dementia, 7.0 for Alzheimer's disease, 1.7 for vascular dementia, 0.53 for dementia with Lewy bodies, 0.74 for Parkinson's disease dementia, 0.21 for progressive supranuclear palsy, 0.11 for frontotemporal lobar degeneration and 0.74 for other dementia. The overall prevalence was higher in women for Alzheimer's disease and Parkinson's disease dementia, and in men, for vascular dementia and dementia with Lewy bodies. ***Conclusion:*** We confirmed the overall prevalence of dementia in the elderly population aged 65 years and older to be 11.0. This finding is higher compared with previous reports in Japan.

Introduction

Examination of the prevalence of dementia is important for health policy planning, especially in developed countries, where the increase in the number of elderly people is striking. In the past, diagnostic criteria and classification methods were not well established. Previously, many epidemiological studies in Japan have focused on only two major dementia subtypes: Alzheimer's disease (AD) and vascular dementia (VD) [1–5]. We investigated the prevalence of dementing disorders in a rural island town of Japan using a door-to-door survey focusing on various subtypes of dementia.

Methods

This study was carried out in the municipality of Ama-cho (approximately 33.5 km^2), a rural island town located 70 km from Yonago city, in the northwestern part of Japan (fig. 1). In 1904, 7 villages were integrated into Ama-son as a village, and the village was promoted to Ama-cho as a town in 1968. Three public health nurses working as permanent care providers had kept detailed information about the physical and mental health of the entire town for over 20 years. For about 30 years, board-certificated neurologists visited this town to examine dementia patients with public health nurses. Before this study, 3 public health nurses received repeated lectures regarding dementia and related disorders from board-certificated neurologists (K.W.-I., K.N). Thus, these

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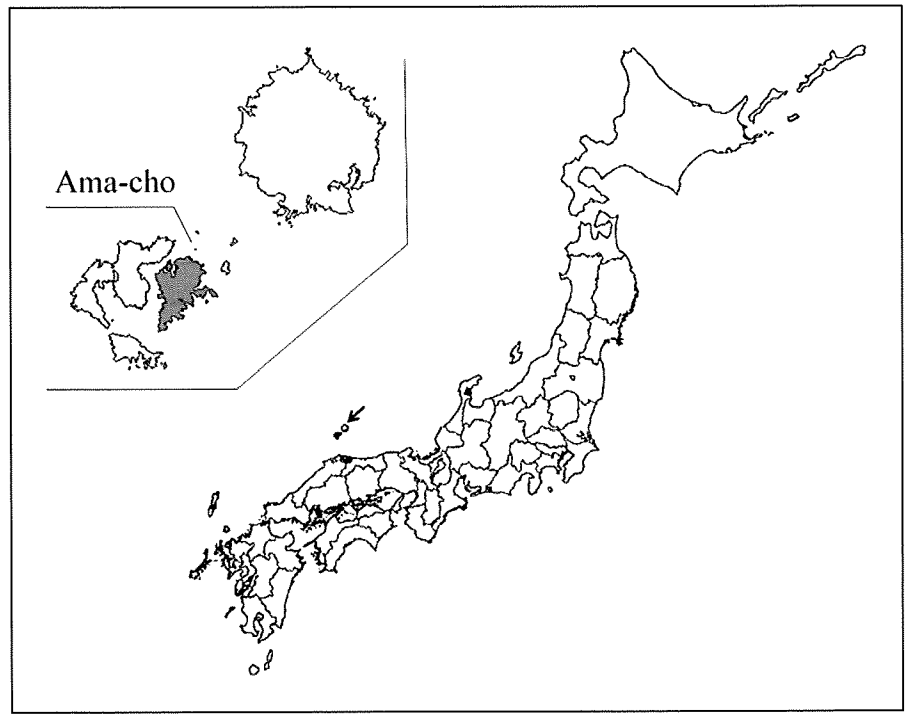

Fig. 1. Geographic location of Ama-cho. Ama-cho is a rural island town located 70 km from Yonago city (circle). The arrow indicates the direction of Oki, consisting of 3 towns and 1 village. An expanded map of Ama-cho is indicated on the left.

public health nurses were well educated and had sufficient knowledge of dementia. To be included in the study, subjects were required to be living and to be legally residing in the town on the prevalence day, 1 March 2008. The total population of Ama-cho in 2008 was 2,430 (1,145 men and 1,285 women). The number of elderly people aged 65 years and older was 943 (386 men and 557 women), or 38.4% of the total population.

In phase 1 of the study, a brief screening of all people aged 65 years and older was administered by the public health nurses in town. The screening included an interview with both subjects and their family that surveyed cognitive changes, psychiatric symptoms, personality changes, problem behaviors, activities of daily living, psychological and medical symptoms. This information was then compared with the subjects' medical history which was offered by the home doctors of the subjects. Those subjects who were suspected of having cognitive impairment sufficiently severe to impair social or professional life, were selected for phase 2 assessment.

In phase 2 of the study, the subjects who showed cognitive impairment in phase 1 were examined to confirm or exclude the presence of dementia and to classify the type of dementia. All subjects in phase 2 were examined by board-certificated neurologists. Assessment of these subjects involved a careful study of medical history, physical examination, including a drug inventory, a neurological examination, a comprehensive cognitive evaluation using the Mini-Mental State Examination [6] and the Blessed Dementia Score [7], activity of daily life evaluation with the Barthel Index [8], a psychosocial assessment of the patient's environment and routine laboratory tests. The subjects in phase 2 were asked to undergo brain computed tomography (CT) in several hospitals for diagnosis, and only a small number of subjects performed magnetic resonance images. Dementia was diagnosed by means of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition revised, criteria [9].

For the patients with dementia, we analyzed the dementing disease using the following criteria: (1) AD was defined according to the criteria of the National Institute of Neurological and Communication Disorders Association [10]; (2) VD was defined according to the criteria of the National Institute of Neurological Disorders and Stroke and the Association International pour la Recherche et l'Enseignement en Neurosciences [11]; (3) dementia with Lewy bodies (DLB) was defined according to the consensus guideline for clinical diagnosis of DLB [12]; (4) Parkinson's disease dementia (PDD) was defined according to the clinical diagnostic criteria for dementia-associated Parkinson's disease [13]; (5) progressive supranuclear palsy (PSP) was defined according to the National Institute of Neurological Disorders and the Society for PSP [14]; (6) frontotemporal lobar degeneration (FTLD) was defined according to international criteria [15]. We excluded cases of cognitive decline secondary to major depression and other mental disorders like schizophrenia only if these were proven to be the main cause for cognitive decline through a psychiatric interview and medical history. Severity of dementia was assessed according to a functional assessment staging of Alzheimer's disease (FAST) [16], as follows: FAST4 = mild, FAST5 = moderate, and FAST6/7 = severe.

We examined all the subjects directly in phase 2 of the study. Prevalence and 95% confidence intervals (CIs) were calculated for all types of dementia and for specific dementing disorders.

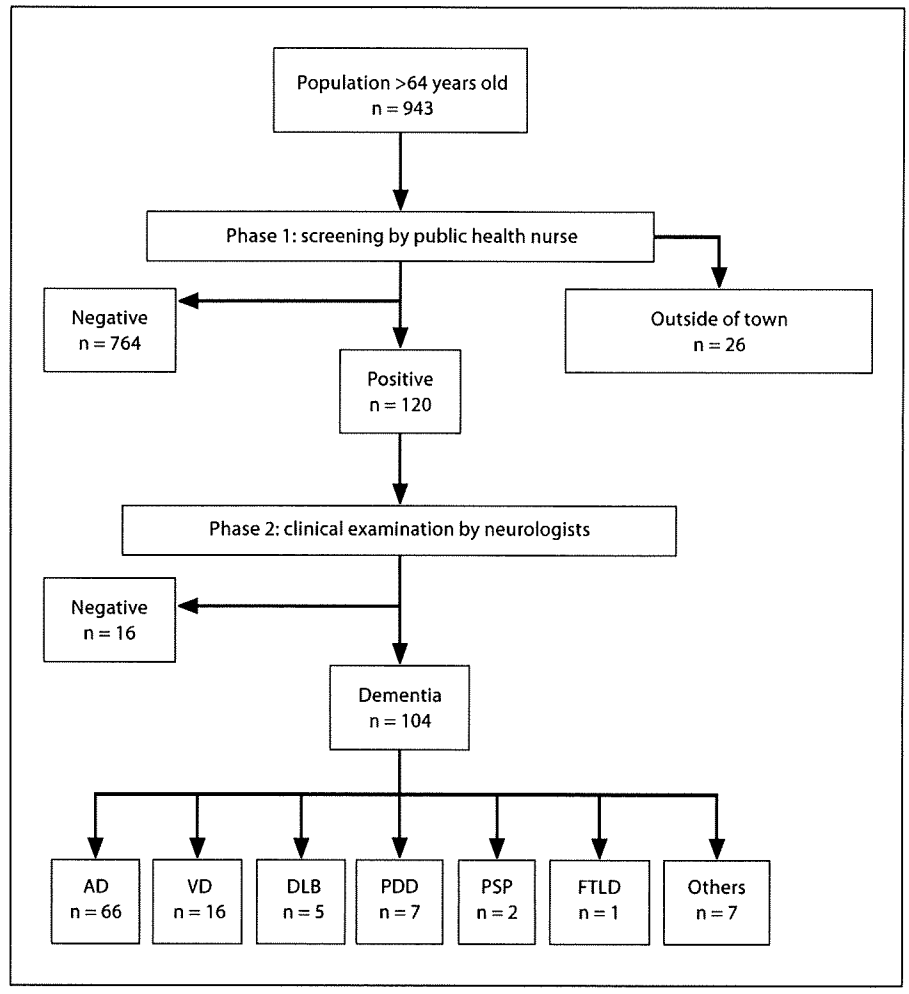

Fig. 2. General design of the door-to-door 2-phase prevalence survey in Ama-cho. The number of subjects involved in each step is shown.

Results

Figure 2 shows the general design of the door-to-door 2-phase prevalence survey. The study population included 943 subjects aged 65 years and older residing in Amacho on the prevalence day. On the prevalence day, 26 subjects (2.8%) were living outside the town.

One hundred and twenty subjects were detected as having cognitive impairment in phase 1 of the study. A total of 104 subjects (33 men, 71 women) fulfilled the diagnosis criteria of dementia, yielding a prevalence for all dementia of 11.0 cases/100 persons aged 65 years and older (95% CI 9.0–13.0). The mean age was 81.6 ± 7.1 years (range 69–93) for men and 85.0 ± 7.0 years (range 65–100) for women. Table 1 shows the number and prevalence of each dementia subtype. The age-specific prevalence of dementia increased exponentially with advancing age for women. However, for men, the prevalence was highest between 70 and 74 years. The prevalence was higher in women than in men in all ages except between 70 and 74 years. The age-adjusted prevalence for dementia by direct method in those aged 65 years and older compared with the population structure of Japan in 2004 was estimated to be 8.8 according to the data from this study.

Of the 104 demented subjects, 66 (63.5%) were diagnosed with AD (12 men, 54 women), 16 (15.4%) with VD (7 men, 9 women), 5 (4.8%) with DLB (3 men, 2 women), 7 (6.7%) with PDD (2 men, 5 women), 2 (1.9%) with PSP (2 men), and 1 (0.96%) with FTLD (1 man). Seven (6.7%) were diagnosed with mixed (1 man) or other dementia not classifiable (5 men, 1 woman). The overall prevalence was 7.0 (95% CI 5.4–8.6) for AD and 1.7 (95% CI 0.87–2.5) for VD. The prevalence of AD was 3 times higher in women than in men, while that of VD was higher in men than in women. The AD/VD ratio was 9.0 in women and 1.7

Table 1. Age- and sex-specific prevalence of dementia

	Population at risk	All types		AD		VD		DLB		PDD		PSP		FTLD		Others	
		cases	prevalence	cases	prevalence	cases	prevalence	cases	prevalence	cases	prevalence	cases	prevalence	cases	prevalence	cases	prevalence
Both sexes																	
65–69 years	178	2	1.1	–	–	1	0.56	–	–	1	0.56	–	–	–	–	–	–
70–74 years	206	10	4.9	4	1.9	4	1.9	–	–	–	–	–	–	1	0.49	1	0.49
75–79 years	226	19	8.4	10	4.4	4	1.8	1	0.44	1	0.44	–	–	–	–	3	1.3
80–84 years	161	22	13.7	16	9.9	2	1.2	1	0.62	–	–	2	1.2	–	–	1	0.62
85–89 years	114	27	23.7	18	15.8	1	0.88	3	2.6	4	3.5	–	–	–	–	1	0.88
90– years	58	24	41.4	18	31.0	4	6.9	–	–	1	1.72	–	–	–	–	1	1.7
Total	943	104	11.0	66	7.0	16	1.7	5	0.53	7	0.74	2	0.21	1	0.11	7	0.74
Men																	
65–69 years	87	1	1.2	–	–	–	–	–	–	1	1.2	–	–	–	–	–	–
70–74 years	90	6	6.7	2	2.2	2	2.2	–	–	–	–	–	–	1	1.1	1	1.1
75–79 years	99	8	8.1	2	2.0	2	2.0	1	1.0	–	–	–	–	–	–	3	3.0
80–84 years	52	6	11.5	2	3.8	2	3.8	–	–	–	–	2	3.9	–	–	–	–
85–89 years	43	7	16.3	2	4.7	1	2.3	2	4.7	1	2.3	–	–	–	–	1	2.3
90– years	15	5	33.3	4	26.7	–	–	–	–	–	–	–	–	–	–	1	6.7
Total	386	33	8.5	12	3.1	7	1.8	3	0.78	2	0.52	2	0.52	1	0.26	6	1.6
Women																	
65–69 years	91	1	1.1	–	–	1	1.1	–	–	–	–	–	–	–	–	–	–
70–74 years	116	4	3.4	2	1.7	2	1.7	–	–	–	–	–	–	–	–	–	–
75–79 years	127	11	8.7	8	6.3	2	1.6	–	–	1	0.79	–	–	–	–	–	–
80–84 years	109	16	14.7	14	12.8	–	–	1	0.92	–	–	–	–	–	–	1	0.92
85–89 years	71	20	28.2	16	22.5	–	–	1	1.4	3	4.2	–	–	–	–	–	–
90– years	43	19	44.2	14	32.6	4	9.3	–	–	1	2.3	–	–	–	–	–	–
Total	557	71	12.7	54	9.7	9	1.6	2	0.36	5	0.90	–	–	–	–	1	0.18

Prevalence = cases/100.

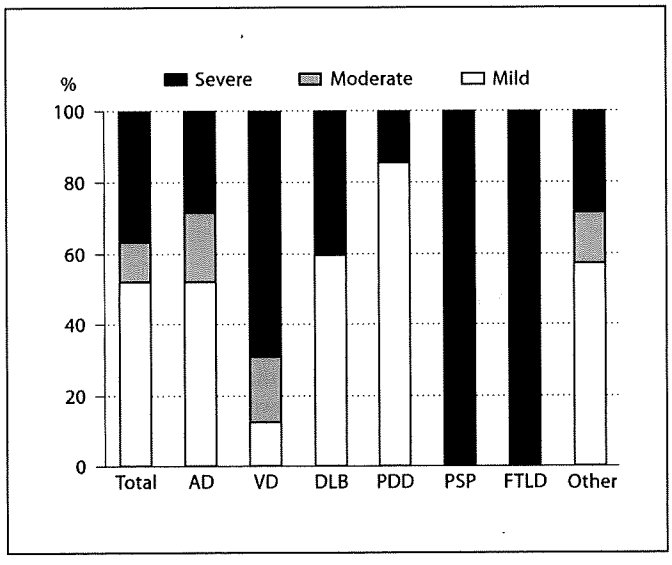

Fig. 3. Severity of subtypes of dementia.

in men. The prevalence was 0.53 (95% CI 0.07–0.99) for DLB and 0.74 (95% CI 0.19–1.3) for PDD. The AD/DLB ratio in both sexes was 13.2. The severity of dementia according to FAST is shown in figure 3. Fifty-four (52.0%) were at the mild stage, 12 (11.5%) at the moderate stage, and 38 (36.5%) were at the severe stage. In AD, most subjects were at the mild stage; however, in VD, most subjects were at the severe stage. Fifty-four (52%) were living in their home and 50 (48%) were living in a nursing home in town.

Discussion

We investigated the prevalence of dementia in an isolated rural island community in western Japan. We selected this town for the following reasons: (1) the public health nurses working as the sole permanent care providers have been keeping detailed information about the physical and mental health of the entire town for over 20

years; (2) active collaboration was offered by family doctors in the town; (3) this town is a rural island with a stable population, and only a few demented subjects move to nursing homes in other areas.

Our study showed that the prevalence of all types of dementia in the elderly population aged 65 years and older was 11.0 in a rural community in Japan. This finding is higher than that of previous Japanese reports showing a prevalence of 3.8–8.5 [3–5, 17–19]. There are some possible reasons for the higher prevalence of dementia found in our study. The first is the relatively higher proportion of subjects in the population aged 65 years and older in the town studied. Second, we surveyed all the demented subjects including those instituted in the nursing home in town, where severely demented subjects are living. Thus, our study indicated a relatively higher prevalence of subjects with severe dementia. Third, we achieved a very high response rate in this survey, due to the outstanding contribution of the public health nurses.

In agreement with recent epidemiological studies in Japan, our study showed that AD is the most common and VD is the second most common subtype of dementia amongst all types of dementia in elderly people [3–5,17, 19]. We also examined the prevalence of subtypes of dementia other than AD and VD. The prevalence was 0.53 for DLB in our study. Some epidemiologic data on DLB are available from a community-based survey. The prevalence of DLB in the general population is reported to be from 0 to 5 [20]. Yamada et al. [17] reported that the prevalence of DLB in Japan among subjects aged 65 years and older was 0.1. Yokota et al. [21] reported the AD/DLB ratio to be 12.9 in their study based on a hospital memory clinic in Japan. The AD/DLB ratio in our study was 13.2, which was consistent with their study. We also examined the prevalence of PDD in the same community. Although several studies found a prevalence of DLB or PDD, few have reported a simultaneous prevalence in a community. DLB and PDD share many pathological and clinical features [22]. The time course of the symptoms and presenting features primarily differentiate these disorders. In this study, the 1-year rule between the onset of dementia and parkinsonism was adapted to distinguish between DLB and PDD. The PDD patients were reliably diagnosed amongst PD patients who had been diagnosed by the UK PD Brain Bank clinical diagnostic criteria [23]. In our study, the prevalence of PDD was 0.74, which was higher than that of DLB. After a systematic review, Arsland et al. [24] reported a 0.2–0.5 prevalence of PDD in the general population. Our results appear to be consistent with this finding.

Only 1 subject was diagnosed as having FTLD in our study. A high frequency of FTLD patients has been reported amongst subjects aged <65 years, but not in subjects aged 65 years and older in Western countries [25, 26]. After their hospital-based study in Japan, Yokota et al. [21] reported that FTLD was the second most common neurodegenerative dementia following AD amongst those with early-onset dementia, but it was very rare amongst late-onset patients. Among 3,715 subjects >65 years of age, Yamada et al. [17] found that none were diagnosed with FTLD, and Ikeda et al. [18] reported only 2 subjects with FTLD among 1,438 subjects aged >64 years in their community-based study in Japan. Our data are consistent with these community-based studies. There is a lack of valid and reliable methods for screening the core clinical features by which FTLD is usually identified, so FTLD can be difficult to diagnose in the community.

This study is a door-to-door, 2-phase design based on phase 1 screening by highly educated public health nurses and on phase 2 diagnosis by a neurologist. Some limitations of this study have to be considered. One important limitation was the relatively small size of the population surveyed, and our estimations of subtypes of dementia are based on a small number of cases. Second, we mainly evaluated brain imaging of the subjects by CT scan; however, magnetic resonance imaging detects abnormal findings more sensitively than CT. Third, although all diagnoses in this study were made according to the most recent clinical diagnostic criteria, no patients were neuropathologically diagnosed with subtypes of dementia.

In conclusion, we showed the prevalence of dementia in the elderly population aged 65 years and older in a rural area in Japan to be 11.0 cases/100 population, which is higher than that found by previous epidemiological studies in Japan.

Acknowledgments

We thank all the inhabitants of Ama-cho for their participation in the present study. We also thank Dr. Sakakibara, Dr. Kitagawa, Ms. Hamami, Ms. Nakagawa, Ms. Ikeda and Ms. Yoshino for collecting and providing clinical information. This study was supported, in part, by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Government of Japan (to K.N.).

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Original Paper

Neuro
epidemiology

Neuroepidemiology 2009;32:263–269
DOI: 10.1159/000201565

Received: July 14, 2008
Accepted: December 8, 2008
Published online: February 11, 2009

Changes in Prevalence and Incidence of Parkinson's Disease in Japan during a Quarter of a Century

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Key Words
Parkinson's disease · Epidemiology · Japan

Abstract
Background/Aim: To determine the prevalence and incidence of Parkinson's disease (PD) and compare them with results from our previous studies. ***Methods:*** We examined epidemiological characteristics of PD patients using a service-based study in Yonago City, and a door-to-door study in Daisen Town. The prevalence days were April 1, 2004 in Yonago, and April 1, 2003 in Daisen. ***Results:*** In Yonago, we identified 254 PD patients. The crude prevalence was 180.3 (95% CI, 158.1–202.4) per 100,000 population. The adjusted prevalence was 145.8 (95% CI, 145.2–146.5) in 1980, 147.0 (95% CI, 146.3–147.6) in 1992, and 166.8 (95% CI, 166.1–167.5) in 2004, when calculated using the Japanese population in 2004. The crude incidence was 18.4 (95% CI, 11.3–25.5) per 100,000 population per year. The crude incidence in 1980 was 10.2 (95% CI, 4.6–15.8), and the adjusted incidence was 9.8 (95% CI, 4.3–15.3) in 1992, and 10.3 (95% CI, 4.7–15.9) in 2004, when calculated using the population in Yonago in 1980. In Daisen, there were 21 PD patients. The crude prevalence was 306.6 (95% CI, 175.7–437.6) and the adjusted prevalence was 192.6 (95% CI, 191.9–193.8). ***Conclusions:*** The prevalence of PD had increased, primarily because the population had aged. Differences in prevalence between these adjacent areas may have resulted from differences in the methods of investigation.

Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative disorders. In 1980 and 1992, we performed epidemiological studies of PD in Yonago City in Japan [1, 2], but there have been few long-term studies of this kind in the same areas. In addition, the prevalence of PD as determined by door-to-door studies may be greater than by other approaches such as service-based studies [3]. We therefore wanted to extend our previous studies longitudinally, using the same methods and diagnostic criteria to determine the prevalence and incidence of PD. Since PD has an insidious onset and slow progression, a clinical diagnosis is especially difficult in the early stages of the disease. We therefore performed the investigation twice. We also attempted to determine why patients diagnosed in the second investigation had escaped notice during the first investigation. Furthermore, we intended

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Table 1. Population and number of patients in Yonago and Daisen

Age	Yonago								
	men			women			total		
	population	cases	prevalence	population	cases	prevalence	population	cases	prevalence
0–39	32,412	–	–	32,128	–	–	64,540	–	–
40–44	4,022	1	24.9	4,262	1	23.5	8,284	2	24.1
45–49	4,332	–	–	4,365	–	–	8,697	–	–
50–54	4,936	2	40.5	5,187	4	77.1	10,123	6	59.3
55–59	5,212	3	57.6	5,477	4	73.0	10,689	7	65.5
60–64	4,296	8	186.2	4,742	14	295.2	9,038	22	243.4
65–69	3,584	7	195.3	4,186	16	382.2	7,770	23	296.0
70–74	3,219	17	528.1	4,072	24	589.4	7,291	41	562.3
75–79	2,530	27	1,067.2	3,835	53	1,382.0	6,365	80	1,256.9
80–84	1,346	12	891.5	2,811	28	996.1	4,157	40	962.2
85–89	586	6	1,023.9	1,559	15	962.2	2,145	21	979.0
90+	310	3	967.7	1,067	9	843.5	1,377	12	871.5
Age unknown	279			156			435		
	67,064	86	128.2	73,847	168	227.5	140,911	254	180.3

Prevalence was defined as the number of PD patients per 100,000 population. – = There were no cases for the age and sex groups.

to compare the results to those from our studies in the neighboring area, Daisen Town, in which we used different methods of investigation. We also used data collected door-to-door to determine the prevalence of PD, and we analyzed differences in results obtained with the different methods of the PD survey.

Methods

Service-Based Study in Yonago

We conducted a service-based study of PD in Yonago, a city in western Japan. During 1980, and from 1992 through 2004, the population increased, from 126,097 at the end of 1980, to 132,315 in 1992, and to 140,911 in 2004. Concurrently, the proportion of those over 65 years of age increased from 10.3% at the end of 1980 to 13.9% in 1992, and 20.7% in 2004. Since 1980, the migration rate had been stable, ranging from 9.2 to 11.0%. There were 12 general hospitals, 118 clinics, 8 geriatric health service facilities, and in addition, the University Hospital to serve as a neurological center. From January to October 2005, and from August 2006 to September 2007, we examined PD patients using the same method as in our previous studies [1, 2]. We recorded the patients' age, age at onset, duration and severity of disease, and complications.

Door-to-Door Study in Daisen

Daisen is located near Yonago. During the previous 12 years, the population decreased from 7,685 in 1991 to 6,849 in 2003, and the proportion of those over 65 years of age increased from 21.5 to 28.0%. We sent questionnaires to all inhabitants over 20 years of age to screen for those who showed symptoms suggestive of parkinsonism. We also conducted searches of patient documentation, including population stroke screening records, records for long-term care insurance, records of bedridden patients, and intractable disease surveys performed by community health nurses. Volunteer health officers in each small community were also interviewed to determine whether they knew of any individuals with parkinsonism in their communities. To confirm the diagnosis of PD, neurologists met with the candidates and their family members, at home or in official daycare centers.

Data Analysis

Diagnoses of PD were based on the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria [4]. Disease severity was described according to the Hoehn and Yahr (H&Y) scale score [5]. Prevalence was defined as the number of PD patients per 100,000 people living in Yonago on April 1, 2004, and in Daisen on April 1, 2003. The crude incidence of PD was defined as the number of new PD cases per 100,000 per year, and was determined as the average for the period from 2000 to 2004 in Yonago. To determine the age- and sex-adjusted prevalence, we used the Japanese population in 2004, and for the age- and sex-adjusted incidence, we used the population of Yonago in 1980.

The mean values for the two groups were analyzed using the Mann-Whitney U test. The mean values for three groups were analyzed using the one-way analysis of variance with a post hoc comparison: Tukey-Kramer test. The difference of the prevalence was evaluated using Fisher's exact test for 10-year intervals up to over 80 years of age. Differences in severity were analyzed using

Daisen									Japan in 2004 (thousand persons)		
men			women			total			men	women	total
population	cases	prevalence	population	cases	prevalence	population	cases	prevalence	population	population	population
1,316	–	–	1,245	–	–	2,561	–	–	30,289	29,166	59,455
187	–	–	183	–	–	370	–	–	3,976	3,933	7,909
228	–	–	219	–	–	447	–	–	3,936	3,918	7,854
311	–	–	306	–	–	617	–	–	4,633	4,667	9,300
279	–	–	245	–	–	524	–	–	4,762	4,878	9,640
211	–	–	202	–	–	413	–	–	4,193	4,459	8,652
192	–	–	250	1	400.0	442	1	226.2	3,484	3,859	7,344
212	3	1,415.1	258	3	1,162.8	470	6	1,276.6	2,951	3,515	6,465
176	2	1,136.4	272	2	735.3	448	4	892.9	2,168	2,930	5,098
88	–	–	206	4	1,941.8	294	4	1,360.5	1,130	2,105	3,235
49	1	2,040.8	123	4	3,252.0	172	5	2,907.0	526	1,193	1,718
23	–	–	68	1	1,470.6	91	1	1,098.9	247	769	1,016
3,272	6	183.4	3,577	15	419.4	6,849	21	306.6	62,295	65,392	127,687

Table 2. Comparison of the two investigations

	Yonago			Daisen
	1st investigation	2nd investigation	total	
Patients	220	34	254	21
Age, years	75.3 ± 9.6	72.9 ± 7.3	75.0 ± 9.3	79.0 ± 7.0
Age at onset, years	68.6 ± 10.7	68.9 ± 7.4	68.7 ± 10.3	72.2 ± 7.7
Duration of illness, years	6.5 ± 5.4	3.4 ± 4.1[1]	6.1 ± 5.3	6.7 ± 6.0
H&Y scale score	3.3 ± 1.0	2.9 ± 1.0[1]	3.3 ± 1.0	3.8 ± 0.9[2]

[1] Significant difference relative to the 1st investigation.
[2] Significant difference relative to results in Yonago (total).

Fisher's exact test. $p < 0.05$ was considered statistically significant. We used the Statistical Package for the Social Sciences v. 15.0 (SPSS, Chicago, Ill., USA).

These studies were approved by the Ethical Review Board of the Tottori University Faculty of Medicine.

Results

Service-Based Study in Yonago

One hundred and seven (77.0%) medical institutions responded in the first investigation and 136 (97.8%) medical institutions responded in the second investigation, which provided us with 254 patients with PD (table 1). Of the 241 patients in the first investigation diagnosed with PD, 21 patients (8.7%) became ineligible in the second investigation by the clinical diagnostic criteria. Thirty-four of the 254 patients (13.4%) were newly diagnosed in the second investigation. The H&Y scale score and mean duration of illness were significantly lower in the second investigation (table 2), and the patients had generally received diagnoses of different disorders at the first investigation or had shown milder motor deterioration and mild symptoms (table 3). Table 2 summarizes the characteristics of the PD patients. There were no significant

Table 3. Summary of the 2nd investigation

	Cases
Different diagnosis at the 1st investigation	15
Essential tremor	2
Other movement disabilities[1]	7
Parkinson syndrome[2]	6
Predominant tremor with little motor deterioration	7
Extremely early stage at the 1st investigation	6
Previously diagnosed[3]	2
Accidental[4]	2
Limited follow-up information	2
Total	34

[1] Such as paralysis by cerebral infarction, osteoarthritis, spinal canal stenosis, and thyropathy.

[2] Including vascular, progressive supranuclear palsy, and drug-induced.

[3] They did not have continual checkups at a medical institution because their motor disorders were mild.

[4] They were incidentally diagnosed after hospitalization for a thigh bone or collum femoris fracture.

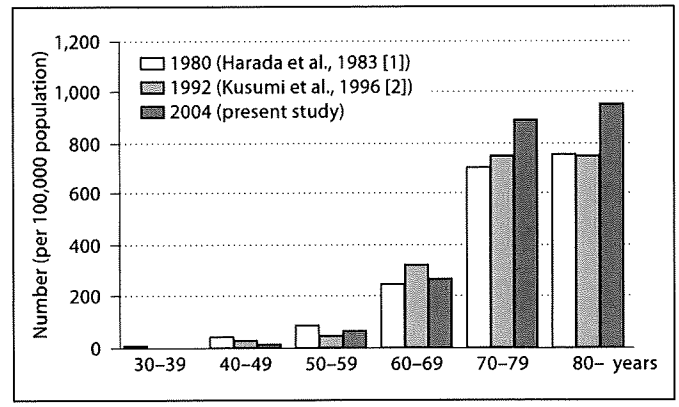

Fig. 1. Comparison of age-specific prevalence of PD. The crude prevalence tended to decrease in those less than 50 years of age, and to increase in those greater than 70 years of age.

gender differences in the patients' mean age (men, 74.1 ± 9.3 years; women, 75.5 ± 9.3 years), mean age at onset (men, 68.0 ± 10.4 years; women, 69.0 ± 10.3 years), duration of illness (data not shown) or H&Y scale score (men, 3.3 ± 1.1; women, 3.3 ± 0.9). There were 3.6% (men, 4.6%; women, 3.0%) of patients with an H&Y scale score of stage I, 15.5% (men, 19.8%; women, 13.3%) in stage II, 41.4% (men, 36.0%; women, 44.3%) in stage III, 27.5% (men, 23.3%; women, 29.7%) in stage IV, and 12.0% (men, 16.3%; women, 9.7%) in stage V. The men and women did not differ significantly in rates of progression. The patients' mean age and the mean age at onset determined in 2004 were significantly increased compared with the values for 1980 and 1992 [1, 2]. There was no significant difference in duration of illness in 2004 as compared with 1992.

The crude prevalence was 180.3 (95% CI, 158.1–202.4), with 128.2 for men (95% CI, 101.2–155.3) and 227.5 for women (95% CI, 193.1–261.9), in 2004. The prevalence for those over 65 years of age was 745.6 (95% CI, 646.8–844.4). There were significant gender differences among patients 50–79 years of age. Figure 1 shows the shifting of the crude prevalence over the three studies. The prevalence for patients over 80 years of age was significantly higher in 2004 than in 1980 and 1992. The age- and sex-adjusted prevalence was 166.8 (95% CI, 166.1–167.5) in 2004. In 1992, the crude prevalence was 117.9 (95% CI, 99.4–136.4), and the age- and sex-adjusted prevalence was 147.0 (95% CI, 146.3–147.6). In 1980, the crude prevalence was 80.6 (95% CI, 64.9–96.3), and the age- and sex-adjusted prevalence was 145.8 (95% CI, 145.2–146.5). Thus, the crude prevalence in 2004 increased when compared with those in 1980 and 1992. Furthermore, the age- and sex-adjusted prevalence in 2004 was also significantly increased (fig. 2a).

In 2004, the crude incidence was 18.4 (95% CI, 11.3–25.5) with 13.8 for men (95% CI, 4.9–22.7) and 22.6 for women (95% CI, 11.8–33.5), and the age- and sex-adjusted incidence was 10.3 (95% CI, 4.7–15.9). In 1992, the crude incidence was 15.0 (95% CI, 8.4–21.6), and the age- and sex-adjusted incidence was 9.8 (95% CI, 4.3–15.3). In 1980, the crude incidence was 10.2 (95% CI, 4.6–15.8) (fig. 2b). The crude incidence increased in 2004, although the age- and sex-adjusted incidence did not change.

Door-to-Door Study in Daisen

Of the 5,828 eligible subjects in the door-to-door study performed in Daisen, 4,765 (81.8%) completed the questionnaire, and 21 patients with PD were found (tables 1, 2). Two patients (9.5%) refused medical treatment, because visiting the hospital would have been difficult as a result of advanced age. There were no significant gender differences in mean age (men, 76.0 ± 5.7; women, 80.1 ± 7.4), mean age at onset (men, 70.1 ± 5.3; women, 72.7 ± 8.7), duration of illness, or H&Y scale score (date not shown).

In 2003, the crude prevalence was 306.6 (95%CI, 175.7–437.6), with 183.4 for men (95% CI, 36.8–330.0) and 419.4

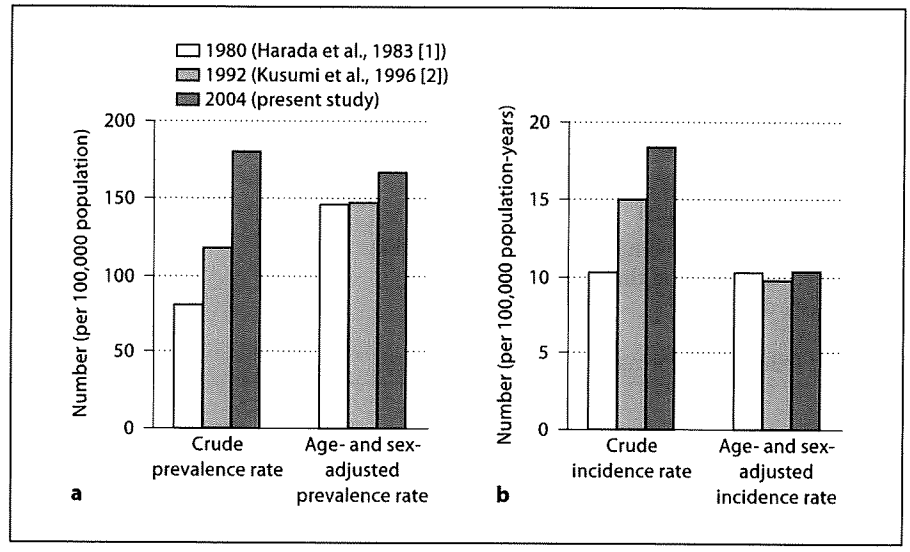

Fig. 2. Comparison of prevalence and incidence of PD. **a** The age- and sex-adjusted prevalence was significantly increased (adjusted to the Japanese population in 2004). **b** The age- and sex-adjusted incidence was not changed (adjusted to the population of Yonago in 1980).

for women (95% CI, 207.6–631.1). The prevalence for those over 65 years of age was 1,095.5 (95% CI, 629.5–1,561.4). The age- and sex-adjusted prevalence was 192.6 (95% CI, 191.9–193.8).

Discussion

This is the first study to investigate changes in the prevalence and incidence of PD in a specific area of Japan over the course of 25 years. In Yonago, we found a higher crude prevalence and incidence in this study than in our previous studies [1, 2]. One factor that contributed to the increase in crude prevalence was the aging of the population, which has been shown to be significant throughout Japan, and is reflected in the data for Yonago [6]. Others have also reported a higher prevalence of PD in the elderly [7–12]. In this study, the overall numbers and prevalence estimates of PD increased with age, confirming a role for the demographic shift. The age- and sex-adjusted prevalence was also significantly increased compared with our previous studies [1, 2]. Although the migration rate may affect prevalence figures, it had not changed during one quarter of a century in Yonago. Consequently, several other factors should be considered in our study. First, the crude prevalence was increased in elderly patients, which may indicate increasing willingness among them to consult physicians for symptoms that were previously regarded as a normal part of aging. Second, the opportunity for patients to be examined by a neurologist may have increased. The number of neurological specialists certified by the Japanese Society of Neurology grew from 14 in 1992 to 27 in 2004, and the increased awareness of PD among personal physicians, through participation in our studies, may have caused them to refer patients with parkinsonism more swiftly. Third, long-term care insurance was introduced in Japan in 2000, and elderly patients were required to undergo checkups at medical institutions in order to qualify. The environmental risk factors related to PD, including exposure to pesticides and herbicides, were reported [13–15]. In Yonago, the population that works in agriculture had decreased but whether the proportion of that population exposed to pesticides and herbicides had also decreased is not known. The contribution of these environmental factors to the observed increases in prevalence remains inconclusive. The age- and sex-adjusted prevalence may have increased as the number of consultations increased.

We found a consistently higher prevalence of PD in women than in men across almost all age groups, which is consistent with other reports in Japan [1, 2, 16, 17]. Haaxma et al. [18] reported that women with PD have a more benign phenotype, and that symptoms may develop more slowly in women because of higher striate dopamine levels, possibly related to estrogen activity. The women preponderance of PD in Japan may therefore reflect a slower rate of progression than in men. Although a significant gender difference in severity did not appear at any point in our study, we did report the slow progression of PD for women in the same area [19]. Differences in the men:women ratio between Japan and Europe may represent genetic and environmental factors that modify the risk.