の流暢性の障害を示している．これはADとの比較においても明らかであり，彼らはDLBとの共通性を主張している[3]．また，RBDはシヌクレイノパチーであるDLBの診断基準の支持症状としても現在あげられている[25]．

以上のようにRBDはPDを中心としたシヌクレイオパチーに高率にみられる．さらにPDやDLBの病前症状として重要な病態であると考えられる．しかし，MSAでも高率にRBDの発症を認めるが，RBDとMSAの症状共通性を示唆する報告は乏しく，今後同様の検討が必要である．

REM睡眠行動障害とその他の神経変性疾患の関連

シヌクレイノパチーの鑑別疾患としてあげられるAlzheimer病，PSP, CBDでは今まで少ないものと考えられていた．しかし，最近PSPにおいてPDとの比較で高頻度みられたという報告[26][27]がある．Arnulfらは，それぞれ15人のPD, PSP, 対照群においてRBD症状がPSPの男性2人(13%)，PDの男性3人(20%)で認め，RWAがPSPではREM睡眠中の33±36%とPDの28±35%とともに高率に認めたと報告している[26]．さらにSixel-Doringらは，PSP 20人中17人でRWAを認め，そのうち7人がRBD症状を呈していたと報告している[27]．彼らは，PSPにおいてもRBD制御部位の障害によりRBDが出現すると考察している．しかし，原発性進行性失語症(primary progressive aphasia)，前頭側頭型認知症(frontotemporal demenita)などの他のタウオパチーでも報告はなく，前述のシヌクレイオパチーの報告に比べると報告が限られており，今後さらなる検討が必要である．

REM睡眠行動障害とその他の神経疾患

RBDはその他の種々の神経疾患において合併が報告されている．とくに自己免疫疾患とも考えられるナルコレプシーではRBDの合併が報告されている[28]．ナルコレプシーでの入眠時幻覚は覚醒時にREM睡眠の介入と考えられ，覚醒時の骨格筋脱力の介入が情動脱力発作や睡眠麻痺と考えられる．RBDはREM睡眠中に骨格筋の脱力障害が起こっており，これら両疾患はREM睡眠中や覚醒時のREM睡眠制御機能の問題と考えられる[4]．

さらにIranzoらは，電位依存性Caチャンネル抗体関連辺縁系脳炎6人中5人にRBDが出現したという報告をしており，機序として自己免疫系と辺縁系の障害の重要性を考察している[29]．RBDの病態として脳幹病変以外にも情動系の症状が夢幻様行動出現には不可欠と考えられるため，RBDの機序として貴重な病態と考えられる．

このようにRBDは，シヌクレイノパチーのみでなくタウオパチー，その他の神経疾患でも認められることがあり，heterogeneousな疾患と考えられる．現在脳幹病変がRWAの出現にかかわっているとの知見が得られているので，今後は辺縁系を中心とした情動系の機序の解明が必要と考えらえる．

おわりに

REM睡眠行動障害(RBD)は今まで睡眠随伴症として診断，治療が行われてきた．続発性のRBDが多岐の神経疾患でみられていたが，特発性RBDがシヌクレイノパチーを中心とした神経変性疾患に進展する症例が多く報告されて以来，シヌクレイノパチーの病前症状として注目されている．しかし，RBDのみの症状で長期間保持される症例も多く，heterogeneousな病態と考えられる．REM sleep without atoniaのみでRBD症状を示さない症例が多数例存在し[6]，さらに非暴力的な夢内容の行動化も神経変性疾患の初期段階である可能性も示摘されているため[30]，今後，さらに続発性RBDを含めた多様なRBD症例の集積が必要である．とくにシヌクレイオパチー，タウオパチーにおいては臨床経過とともに病理学的検討がRBDのParkinson病などのシヌクレイオパチーの病前症状の可能性を確定するためにも重要と考えられる．RBDは神経変性疾患の早期発見，早期治療の手掛かりとなりうる病態だけに注目してさらなる検討が必要である．

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原著

レボドパ投与により眼球運動障害が改善した進行性核上性麻痺の1例*

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Key Words：PSP-parkinsonism, Parkinson disease, levodopa, apraxia of lid opening

はじめに

進行性核上性麻痺(progressive supranuclear palsy：PSP)は，1964年にSteeleらが最初に記載した神経変性疾患で，核上性眼球運動障害，仮性球麻痺，頸部や体幹部に強い筋強剛，および認知症を臨床的特徴とする[1]．典型例ではレボドパ反応性が乏しく，早期に寝たきりになるなどParkinson病(PD)より進行が早い疾患である[1]．PSPには典型例のほかにも亜型が存在すると考えられており，Williamsらは，Richardson's syndrome(RS)，PSP-parkinsonism(PSP-P)，pure akinesia with gait freezing(PAGF)の3亜型を提唱している[2][3]．われわれは，長期間にわたる緩徐進行性の経過をたどり，Parkinson症候群のみならず，眼球運動障害に対してもレボドパ投与が有効であった非定型的Parkinson症候群の1例を経験したので報告する．

症　例

患者：77歳，男性．

主訴：構音障害，動作緩慢．

既往歴，家族歴：特記事項はない．

現病歴：1993年，書字障害が出現した．近医でPDと診断され，ブロモクリプチンを処方されたが，めまいなどの副作用があり休薬した．1997年頃から構音障害が出現した．1999年から立ちくらみがあり，表情が乏しくなり，抗PD薬(抗パ薬)が再開となったが，めまいなどの副作用があったため十分な増量ができず，Parkinson症状に対しては効果を示さなかった．2000年頃からすくみ足やすり足歩行などの歩行障害が出現した．2001年から両側眼瞼攣縮が出現し，Meige syndromeと診断され，ボツリヌス毒素治療を受けたが効果は一時的であった．2005年には嚥下障害が出現した．2006年頃から尿失禁が出現，同時期からものが見えにくいと訴え始めた．レボドパ・カルビドパ350mgに加え，塩酸セレギリン5mg，ロピニロール3mgと抗パ薬を漸増するが徐々に構音障害，嚥下障害が増悪したため，2008年，精査加療目的に当科に入院した．

入院時現症：体温36.9℃，血圧105/54mmHg．胸腹部に異常所見はなく，下腿浮腫は認めなかった．神経学的所見としては意識清明であるが，

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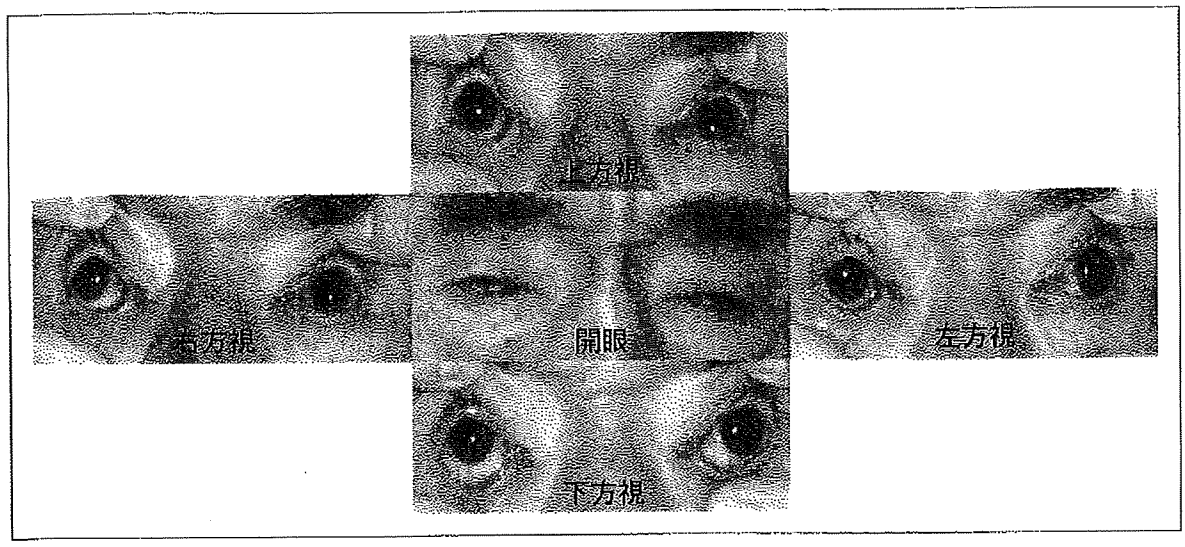

図1 眼球運動
開眼失行，両眼瞼攣縮が認められる．眼球運動は全方向で制限されている．

高度の構音障害や吃音のため，会話は単語レベルに限定されていた．開眼失行があり，閉眼時に眉毛周辺にふれると容易に開眼でき，感覚トリックを示したが，眼球運動時には再び閉眼してしまった．眼球運動は全方向に制限があり(図1)，感覚トリックによる眼球運動障害の改善はなかった．輻輳が不能であったが，人形の目試験は陽性で，水平・垂直とも保たれていた．眼振は認めなかった．顔貌は仮面様で，Myerson徴候陽性であった．高度の嚥下障害を認め，咽頭反射は亢進していた．運動系は四肢麻痺を認めず，腱反射は正常であった．錐体外路症状として，四肢に左右差のない鉛管様固縮を認め，頸部は後屈傾向で強い筋強剛を認めた．運動緩慢があり，前傾前屈位で姿勢反射異常を認めた．歩行は小刻みですくみ現象を伴っていた．運動失調や感覚系の異常は認めなかった．自律神経系では，便秘，排尿障害を認めた．

検査所見：認知機能はMMSE 25点，HDS-R 22点で見当識障害と失計算があり，前頭葉機能評価(FAB)は模倣のみ得点でき，3点であった．血液検査では，電解質，肝機能，腎機能，脂質代謝，糖代謝に異常を認めなかった．心電図は49拍/分，正常洞調律でR-R間隔変動係数は1.49％であった．頭部MRI T1強調画像矢状断(図2)において，脳梁膝部と膨大部を結ぶ直線に平行な線で計測した中脳前後径が12.1mm(正常例14.2±1.0mm, PSP例11.3±2.0mm)[4]，T1強調画像水平断で計測した最大中脳前後径が11.9mm(正常例17～20mm, PSP例11～15mm)[5]であり，軽度ながら中脳萎縮を認めた．橋底部前後長と橋被蓋前後長の比は3.75(PD例3.1±0.3, 発症2年未満PSP例3.8±0.6)[6]，中脳レベルの左右大脳脚幅の和と中脳前後長の比は1.92(PD例1.8±0.1, 発症2年未満PSP例1.9±0.8)[6]であった．橋中部レベルの正中部前後長は21.7mm(PD例24.2±0.9mm, 発症4年以降PSP例21.6±2.0mm)と軽度に萎縮していた[6]．中脳上面の形状は凹型であり，PSPを示唆する所見であった[7]．基底核および視床の萎縮がみられ，大脳脚間部のU字状拡大，第三脳室や側脳室の拡大がみられた．大脳皮質は中等度の萎縮がみられたが，左右差は目立たなかった．MR angiographyでは明らかな異常はなかった．明らかな脳波異常を認めなかった．脳血流シンチグラフィーでは両側前頭葉，側頭葉に血流低下が認められた．[^{123}I] *meta*-iodobenzylguanidine(MIBG)心筋シンチグラフィーでは心臓/縦隔比が，早期像で1.85, 後期像で1.80, 洗い出し率が28.1％であり，明らかな心臓交感神経機能異常を認めなかった．

レボドパ25mg点滴静注テストでは約15分後から変化が表れ，Unified PD Rating Scale(UPDRS) III(運動スコア)における手の開閉，前腕回内・回外，立ち上がり，姿勢，歩行の項目が改善し，点数は55点から47点となった．さらに開眼失行，眼瞼攣縮の改善に伴って眼球運動障害の改善も

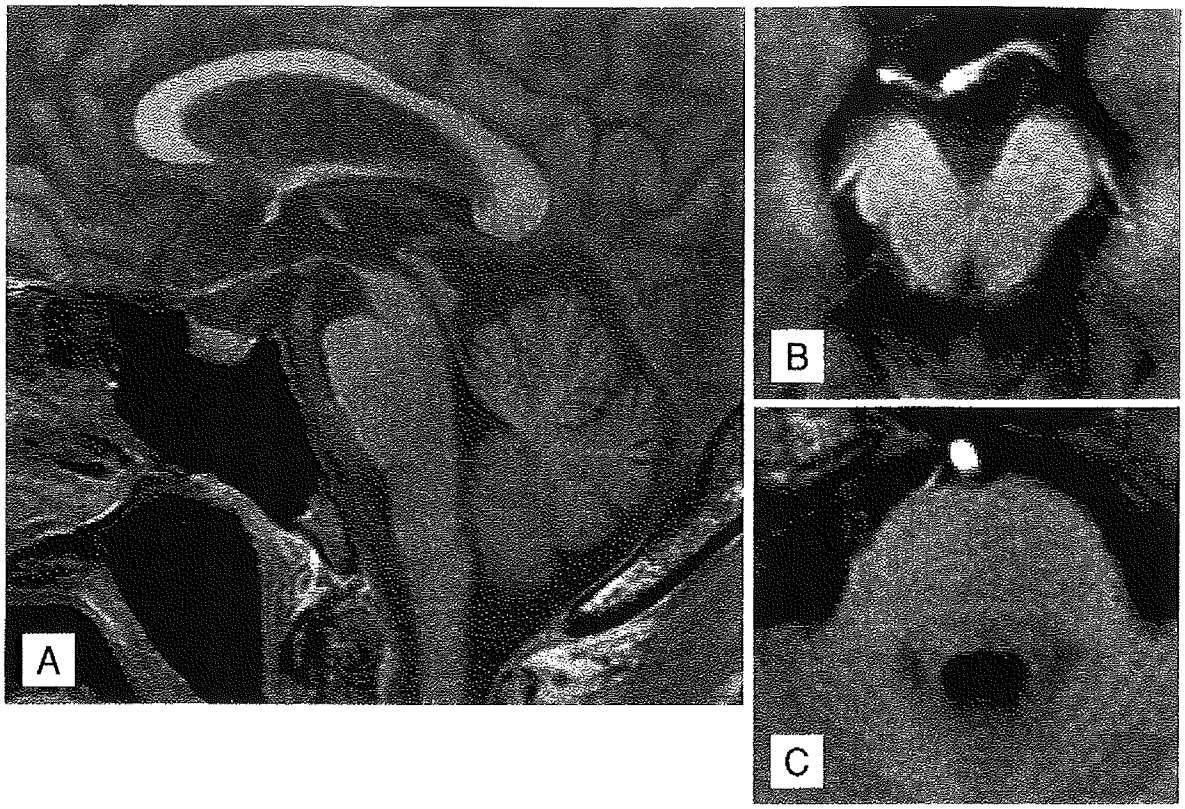

図2　頭部MRI T1強調画像
矢状断(A)では中脳前後径12.1mm，中脳上面の形状が凹型である．水平断(B, C)では中脳前後径が11.9mm，橋中部レベルの正中部前後長は21.7mmであった．

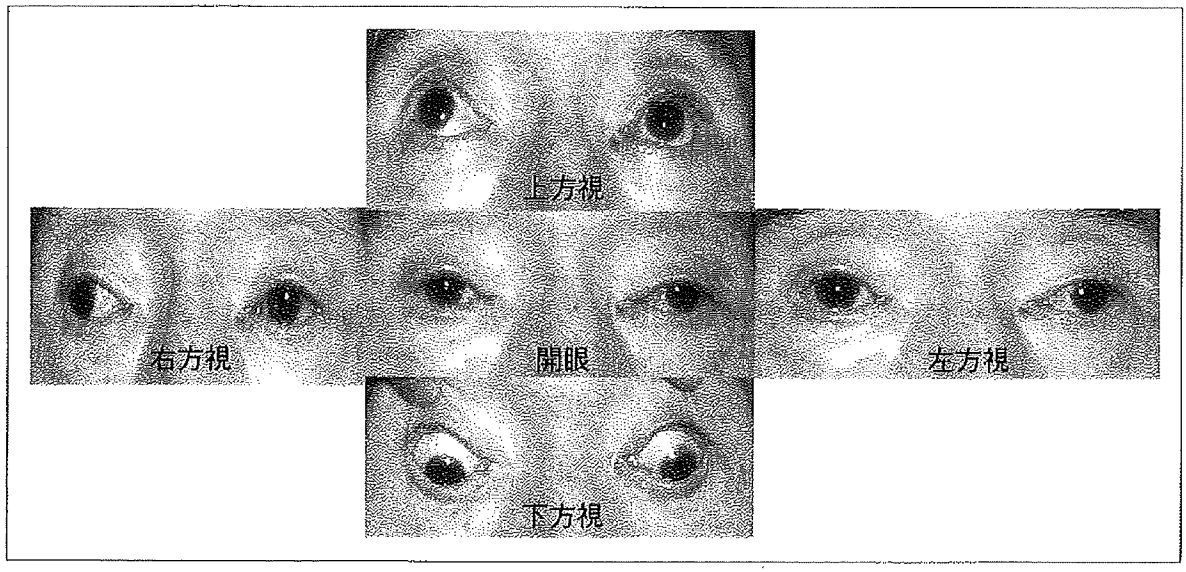

図3　レボドパ25mg静注15分後の眼球運動
開眼失行，両眼瞼攣縮が改善し，開眼可能となった．同時に眼球運動は全方向で改善され，とくに下方視時の改善が著しい．

みられ，全方向とも運動制限が軽快した(図3)．また，構音障害，吃音も改善した．

臨床経過：レボドパ静注が有効であったことから，レボドパ・カルビドパを500mgまで，ロピニロールを6mgまで漸増したところ，Parkinson症状の改善，および眼症状の改善が持続した．しかし，経過中に嚥下性肺炎を併発し，嚥下障害が増悪したため胃瘻造設を行ったうえで自宅

退院となった．

考　察

本例は，15年前に書字障害により発症した緩徐進行性のParkinson症候群で，開眼失行，眼球運動障害を合併していた．臨床症状，画像所見より，多系統萎縮症，Lewy小体型認知症，大脳基底核変性症(CBD)については否定的で，振戦を認めず無動・筋強剛・姿勢反射障害が優位なParkinson症状を呈しており，眼球運動障害を伴っていることより，まずはPSPを考えた．本例ではレボドパによるParkinson症状と眼球運動障害の軽快がみられたが，その改善は部分的であった．また，MIBG心筋シンチグラフィーの結果，および頭部MRIによる中脳被蓋部の萎縮が認められたことからPSPと診断した．

PSPにおける眼球運動障害のレボドパ反応性に関する報告はない．本例では開眼失行や眼瞼攣縮もレボドパ反応性がみられた．開眼失行はPSPの33.3％にみられる症状[8]で，複数の機序が考えられている．Zadikoffらは，眼瞼挙筋の抑制，開眼の無動症状，眼瞼のすくみ現象といった説をあげたうえで，感覚トリックの存在，ボツリヌス毒素治療の有効性などから，純粋な失行よりジストニアの機序を提唱した[9]．開眼失行・眼瞼攣縮の消失と並行して改善のみられた本例の眼球運動障害機序も外眼筋のジストニアなどが考えられるが，詳細は不明である．

本例は臨床的にPSPと診断したが，レボドパ投与によって，眼球運動障害のほか，Parkinson症状の軽快も認め，PDに近い病態を示した症例である．近年，臨床的病理学的検討によりPSPの臨床像を広く捉えようとする考え方があり，典型的PSP例のほかにPSP亜型の臨床像が明らかになりつつある．PSPのうち，RSと呼ばれる典型的な臨床経過をたどるのは約54％であり，約32％の症例は初発症状が非対称的であったり，振戦で発症したり，初期にレボドパ反応性が認められるなど，発症早期においてPDと混同されやすい特徴をもち，PSP-Pとも呼ばれている[2]．罹病期間は，RSでは平均6.3±2.4年なのに対してPSP-Pでは平均11.7±4.9年と有意に長く[10]，死亡年齢はRSでは72.1歳，PSP-Pでは75.5歳と有意に高齢である[2]．また病理学的に，RSでは広範囲にタウ病変が認められ，発症時期が早く，転倒や核上性眼球運動障害，認知症が早期に出現しやすいのに対して，PSP-Pのタウ病変は中脳黒質，視床下核，淡蒼球内節などに限局しており，程度も軽度であると報告されている[11]．本例は経過が長期であることやレボドパが部分的に有効であったことなどからPSP-Pと考えた．

Williamsらは，2007年にPSPの3番目の亜型として，初期に歩行，書字時などのすくみ症状が前景に立つPAGFをあげている[3]が，本例は筋強剛が比較的強く認められ，レボドパ反応性が認められるため，PAGFよりPSP-Pと考えるのが妥当と判断した．

PSP-Pの定義は報告によってさまざまである．Williamsら[2][3]やJellingerら[11]は，病理学的にPSPと診断した症例について後方視的に，臨床症状を基に分類している．本邦においてもPSP-Pに関する報告が散見される[12][13]が，やはり定義は一定していない．坂本らは，PSPによって出現する神経症候の中で，眼球運動障害など他の特異な神経症候に比べてParkinson症状の方が前景に立つ場合をPSP-Pと位置づけ，臨床的にはPD疑いと診断されていたが，剖検ではPSPと診断された症例を報告した[12]．この例ではParkinson症状に対してレボドパが一時的に有効で，眼球運動制限や頸部の筋強剛を認めなかったことから，経過中にPSPと診断することが困難であった[12]．また野田らは，臨床経過から生前にPSP-Pと診断されていた症例について報告し，病理学的にはastrocytic plaqueの存在からCBDと結論づけている[13]．PSP-Pの概念は必ずしも統一されておらず，また，臨床診断基準が明らかでなく，生物学的な診断マーカーが存在しないことが診断をより困難にしており，今後さらなる同様の症例蓄積と解析が必要である．

ま と め

眼球運動障害に対してレボドパが部分的に有効であった進行性核上性麻痺(PSP)の77歳男性例を経験した．PSPの中にはPSP-Pのようにレボドパが有効な例があるため，積極的にレボドパ投与を試みるべきと考える．

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<Abstract>

Improved eye movement by administering levodopa in progressive supranuclear palsy. A case report.

by
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We report the case of a 77-year-old man, who presented with difficulty writing for the last 15 years, and developed akinesia and muscle rigidity accompanied by supranuclear gaze palsy as well as apraxia of eye lid opening. He was diagnosed as having progressive supranuclear palsy (PSP)-parkinsonism, a subtype of PSP, based on his clinical signs and midbrain atrophy seen on MRI. An intravenous levodopa injection partially improved the gaze palsy and the apraxia of eye lid opening as well as his parkinsonism. Given the effects of levodopa, we speculate that his eye movement disturbance might be related to dystonia.

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KEY WORD
●corticobasal degeneration ●clinical diagnostic criteria ●limb-kinetic apraxia ●akinetic-rigid sign ●asymmetry

特集 各論
高齢期のパーキンソン病と類縁疾患

1．高齢期のパーキンソン病の類縁疾患 5）皮質基底核変性症

中島　健二

SUMMARY

■皮質基底核変性症は，①中年以後の高齢者に発症，②緩徐な進行，③肢節運動失行，皮質性感覚障害，他人の手徴候，反射性ミオクローヌスなどの大脳皮質徴候，④無動・筋強剛やジストニアなどの錐体外路徴候，⑤著明な左右差，といった臨床的な特徴を示す疾患である．しかし，非典型的な臨床徴候を示す例も多い．いまだ根治的な治療法はなく，治療は対症療法にとどまる．

はじめに

皮質基底核変性症(corticobasal degeneration：CBD)は，Rebeizら(1968)によりcorticodentatonigral degeneration with neuronal achromasiaとして3例の臨床病理学的な報告がなされたことに始まる[1]．1989年になって，Gibbらは3例の臨床病理学的報告を行い，corticobasal degenerationと呼んだ[2]．その後，報告が相次ぐようになってきている．

発症年齢，罹病期間

発症年齢は40～80歳代で，平均60歳代とされ，中年以降に多い疾患である[3-6]．罹病期間は平均6年程度とされている[3-6]．

病理学的特徴

本症は，前頭・頭頂葉に強い大脳皮質萎縮とともに，黒質・淡蒼球を中心とした皮質下神経核の神経細胞が減少する．神経細胞やグリア細胞に異常リン酸化タウ蛋白が蓄積し，本症はタウオパチーに含まれる[3,7]．顕微鏡学的には，astrocytic plaqueがCBDに特徴的である[3,7]．

症状

左右差のある大脳皮質徴候と錐体外路徴候を特徴とする[3,7]．

大脳皮質徴候として，肢節運動失行，観念運動失行，構成失行，他人の手徴候，把握反射，失語，半側空間無視などが認められる．これらの中でも多くみられ，特徴的な症状は肢節運動失行である[3]．

認知症は，皮質下性認知症の特徴を示すことが多いが，後に皮質性認知症が加わったり，また，初期から皮質性認知症が目立つ例もある[7]．進行すると，構音障害や嚥下障害も出現し，眼球運動障害や錐体路徴候もみられる[3,4]．

錐体外路徴候としてパーキンソニズムがみられる．なかでも，筋強剛が多く観察される[3,6]．振戦は6～8 Hzのことが多く，パーキンソン病と異なり，不規則でjerkyな傾向を示す[3]．静止時振戦を示すことは少ない[7]．ミオクローヌスも振戦とともに観察される．左右差のあるジストニアもみられ，上肢優位の傾向を示す[3,4,6]．進行すると姿勢反射障害や易転倒性が生じる．

臨床検査

頭部の画像検査などでも初期には明らかでないことも多いが，進行すると左右差が観察され，

■なかしま　けんじ(鳥取大学医学部脳神経医科学講座脳神経内科分野)

表1a　難病情報センターによるパーキンソン病関連疾患(大脳皮質基底核変性症)認定基準[3]

1　主要項目

(1) 中年期以降に発症し緩徐に進行する.

(2) 失行あるいはそのほかの大脳皮質徴候
① 肢節運動失行があり，左右差が目立つ.
② 肢節運動失行が明瞭でなくても，皮質性感覚障害，把握反応，「他人の手」徴候，反射性ミオクローヌスのいずれかがあり，左右差が目立つ.
③ 観念運動失行が肢節運動失行よりも顕著な場合は，左右差は目立たないことが多い.
④ そのほかの認知機能障害(まれに，認知症，異常行動，注意障害，失語などが早期から目立つ例がある).

(3) 錐体外路徴候
① パーキンソニズム(無動，筋強剛，振戦)：障害は下肢よりも上肢に目立つことが多い.
② ジストニー

(4) そのほかの神経症状
① 偽性球麻痺(構音障害，嚥下障害)
② 尿失禁

(5) 画像所見
CT，MRI，SPECTで，一側優位性の障害(大脳半球の萎縮または血流低下)は診断において，重要な支持的所見である．しかし，両側性あるいはびまん性に異常所見が出現する例もあるので，診断上必須所見とはしない.

(6) 除外すべき疾患
① パーキンソン病
② 進行性核上性麻痺
③ 多系統萎縮症(特に線条体黒質変性症)
④ 薬剤，脳炎，脳血管障害，外傷など
⑤ 類似症状を呈するそのほかの疾患

(7) 判定
次の3条件を満たすものを皮質基底核変性症と診断する.
① (1)を満たす.
② (2)の1項目以上，および(3)の1項目以上がある.
③ ほかの疾患を除外できる.
注：なお，必須ではないが，画像所見によってほかの疾患を除外し，一側性優位性の障害を確認することが望ましい.

前頭葉や頭頂葉などの非対称性大脳萎縮が観察される[3,6,7]．脳波検査においても，症候優位側との対側に優位な徐波化が観察される[3,6]．しかし，神経症候の左右差が著しい場合であっても，画像検査などでは，びまん性の脳萎縮のみを示す場合もある[6,7]．

診断

CBDは，①中年以後の高齢者に発症し，②緩徐な進行を示し，③大脳皮質徴候として肢節運動失行，観念運動性失行，皮質性感覚障害，他人の手徴候，などが出現し，④錐体外路徴候として無動，筋強剛，ジストニアなどがみられ，

表 1b　難病情報センターによるパーキンソン病関連疾患(大脳皮質基底核変性症)認定基準[3]

2　参考所見

大脳皮質基底核変性症(CBD)は，一側優位性が目立つ大脳半球萎縮および基底核変性を生じる神経変性疾患で，特有の大脳皮質症状と運動障害を呈する．

(1) 臨床的には，以下の所見がみられる．

① 中年期以降に発病し緩徐に進行する．

② 大脳皮質症状として，前頭・頭頂葉症状がみられる．最も頻度が高く特徴的な症状は肢節運動失行で，このほかに観念運動失行，皮質性感覚障害，把握反応，他人の手徴候，反射性ミオクローヌスなどが出現する．

③ 錐体外路症状として，パーキンソニズム(無動，筋強剛，振戦)，ジストニーなどが出現する．症状は下肢よりも上肢の方が顕著なことが多い．

④ 上記神経症状には，病初期から顕著な一側優位性がみられることが多い．

⑤ 注意障害，認知症，異常行動のような精神症状は，通常，運動症状よりも遅れて出現する．

⑥ 歩行障害，偽性球麻痺(構音障害，嚥下障害)などが早期から出現するために，進行性核上性麻痺と鑑別困難な症例がある．

(2) 画像所見

CT，MRI，SPECT で，一側優位性の大脳半球萎縮または血流低下を認めた場合には，重要な支持的所見である．しかし，両側性あるいはびまん性の異常を認める例もあるので，診断上必須所見とはしない．

(3) 薬物などへの反応

L-ドパやほかの抗パーキンソン病薬への反応は不良である．抗うつ薬，ドロキシドパ，経頭蓋磁気刺激などが試みられているが，効果はあっても一時的である．

(4) 病理学的所見

前頭・頭頂葉に目立つ大脳皮質萎縮が認められ，黒質の色素は減少している．顕微鏡的には皮質，皮質下，脳幹の諸核(視床，淡蒼球，線条体，視床下核，黒質，中脳被蓋など)に神経細胞減少とグリオーシスが認められる．ピック細胞と同様の腫大した神経細胞が大脳皮質および皮質下諸核に認められる．黒質細胞には神経原線維変化がみられる．ガリアス染色やタウ染色ではグリア細胞にも広範な変性が認められ，特に astrocytic plaque は本症に特徴的である．

⑤著明な左右差を示す疾患である[3,4,6,7]．しかし，左右差のない例，認知症が目立つ例，進行性核上性麻痺に臨床的に極めて類似した例など，非典型例も多く[3,8]，注意を要する．

わが国では，CBD は特定疾患として指定されており，難病情報センター[3]からその認定基準が示されている(表 1a，b)．また，本邦では森松らにより本症の患者数調査がなされており，その際に用いられた診断基準を表 2 に示す[6]．

Litvan ら(1997) は，古典的な診断基準について病理学的所見との比較検討を行い，発症後 68 カ月後の診察時で感度 48.3%，特異度 99.6%と報告した[9]．すなわち，診断基準に合致すれば CBD であるが，診断基準に合致しない例も約半数存在することを報告している[6,8]．

治療

根治療法はなく，対症療法が基本である[3]．無動・筋強剛などのパーキンソン症状に対しては，L-dopa などの抗パーキンソン病薬が投与される[3,6,7]．しかし，著明な効果は期待し難く，効果は一時的なことが多い[3]．ミオクローヌスに対しては，クロナゼパムなどのベンゾジアゼピン系薬剤が試みられる[3,6,7]．

表2　厚生科学研究事業“神経変性疾患に関する研究班(田代邦雄班長)”による大脳皮質基底核変性症(CBD)の臨床診断基準(暫定)[6]

“probable CBD”：以下の(A)(B)(C)のいずれかに該当するもの

(A)古典型：(1)～(3)のすべてを満たす
(1)緩徐進行性の神経変性疾患(画像的に他疾患を除外する)
(2)以下のaおよびbが一側優位性に出現する
a. 大脳皮質徴候として肢節運動失行
b. 錐体外路徴候として無動・筋強剛
(3)認知症は遅れて出現する
(注)CT, MRI, SPECTを含む画像検査で一側優位性の障害(大脳半球の萎縮または血流・代謝障害)は診断上，重要な支持的所見であるが，びまん性の萎縮または血流・代謝障害の例もあるので，診断上必須所見とはしない

(B)準古典型：ほぼ古典型に似るが，一部条件を満たさないもの．ただし(1)～(3)のすべてを満たす
(1)緩徐進行性の神経変性疾患(画像的に他疾患を除外する)
(2)以下のaまたは(および)bが一側優位性に出現する
a. 大脳皮質徴候として肢節運動失行が明瞭でなくても，皮質性感覚障害，把握反応，他人の手徴候，反射性ミオクローヌスのいずれかを示す．ただし，肢節運動失行よりも観念運動失行が顕著な場合は通常，両上肢に出現する
b. 錐体外路徴候として無動・筋強剛がなくてもジストニー，振戦を示す
(3)認知症は遅れて出現する

(C)非古典型：(1)(2)を満たす
(1)緩徐進行性の神経変性疾患(画像的に他疾患を除外する)
(2)早期には失語，注意障害・異常行動，認知症，尿失禁，偽性球麻痺などの皮質徴候または運動徴候が目立つが，やがて(A)(B)に示した大脳皮質徴候および錐体外路徴候の両者が一側優位性に出現する

“definite CBD”：病理学的にCBDに該当するもの，臨床徴候は問わない
“possible CBD”：資料不足により現状では設けない

リハビリ

廃用性萎縮予防，筋力維持訓練，関節可動域(ROM)の維持訓練，歩行訓練や移動練習，日常生活動作訓練，嚥下訓練などのリハビリテーションが行われる[3]．

生活上の注意

歩行障害，易転倒性に注意する．嚥下障害が著明になると低栄養になって全身衰弱を来し，また，嚥下性肺炎が生じやすくなる．このような場合には，経皮内視鏡胃瘻造設術(PEG)も考慮される[3,7]．

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Age at onset influences on wide-ranged clinical features of sporadic amyotrophic lateral sclerosis

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ABSTRACT

Purpose: To profile the detailed clinical features of sporadic amyotrophic lateral sclerosis (ALS) on large-scale samples in Japan.
Methods: We assessed the clinical features of sporadic ALS patients in Japan, based on the nationwide registration system of the Ministry of Health, Labor and Welfare of Japan. We described 3428 new cases registered cases between 2003 and 2006 to analyze initial symptoms and related clinical features, 4202 cases registered in the single year of 2005 to describe the cross-sectional overview of the ALS patients, and a total of 2128 cases with tracheostomy positive pressure ventilation (TPPV) from all of the registration data from 2003 to 2006 to describe the features of ALS patients with TPPV.
Results: The patients with an older age at onset progressed more rapidly to the TPPV stage than those with a younger age at onset. The subpopulation of patients with long-standing TPPV showed ophthalmoplegia, while its appearance rate was less in the patients with an older age at onset than in those with a younger age at onset. Furthermore, age at onset strongly influenced the frequency of initial symptoms: dysarthria, dysphagia, neck weakness and respiratory disturbance were more frequent in patients with an older age at onset, while upper or lower limb weakness was observed more frequently in patients with a younger age at onset. In addition, those initial symptoms were still the most prominent at the follow-up stage, suggesting that the initial symptoms determine the major clinical features even in advanced illness.
Conclusions: Our present study demonstrated that symptomatic features of ALS are strongly influenced by the age at onset by the large scale of samples.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is one of the most devastating neurodegenerative diseases affecting upper and lower motor neurons preferentially, and shows progressive muscle wasting of the limb, bulbar and respiratory musculatures. Almost half of ALS patients expire within three years of onset, primarily due to respiratory failure [1–6]. Approximately 5–10% of ALS patients show a familial trait, while more than 90% of the patients are sporadic, and the causal mechanism of the motor neuron degeneration is largely unknown. Although many clinical trials of potential therapeutic agents for the treatment of sporadic ALS have been performed [7], effective therapeutics against motor neuron degeneration in ALS except for riluzole [8,9] have not been developed. The clinical features of ALS have been established for the most part. However, many aspects of symptomatic manifestations such as the influence of age at onset on clinical features, the frequency of rare symptoms and many other symptomatic details have not been well characterized, particularly

Abbreviations: ALS, amyotrophic lateral sclerosis; TPPV, tracheostomy positive pressure ventilation.

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based on a nationwide scale sample. In Japan, the proportion of the ALS patients with TPPV is relatively higher than in other countries [10,11]. Rare symptoms such as ophthalmoplegia are more frequently seen in those who receive TPPV to prolong survival [12,13], so the clinical profile of ALS patients in Japan might have unique features. Data concerning the clinical features are important to establish an early diagnosis, treatment plan, and prognostic estimation, as well as to design clinical trials.

The aim of this study was to profile the detailed clinical features of sporadic ALS on large-scale samples in Japan.

2. Research design and methods

A nationwide registration of patients with intractable diseases including ALS has been conducted by the Ministry of Health, Labor and Welfare of Japan since 1974. When a patient is diagnosed as having ALS, the patient can apply for registration in this system, and receive financial support from the state for medical expenses incurred for the treatment of ALS, independent of the disease severity. In 2003, a data collection system was developed for research use of this registration system. Concurrently with that, the registration form for ALS was revised substantially. Since 2003, the annual renewal of registration of each patient has been conducted. The data from registration forms were input to the database in each prefectural office and consolidated in the Ministry of Welfare, Health and Labor of Japan. In the revised registration form, the overview of the clinical state is to be indicated, including the severity, neurological symptoms, activities of daily living and conditions of tube feeding or non-invasive positive pressure ventilation (NIPPV) and TPPV of ALS patients in Japan on a nationwide scale. Using the data accumulated from 2003 to 2006, we analyzed the clinical features of sporadic ALS patients in Japan. Clinical profiles of sporadic ataxias in Japan were previously described using this registration system [14].

The inclusion criteria of the registration system for ALS are: 1) adult onset, steady progressive course; 2) the presence of clinical or electrophysiological evidence of lower motor neuron (LMN) degeneration in at least two topographical anatomic regions (brainstem, cervical, thoracic or lumbosacral region), together with clinical evidence of upper motor neuron (UMN) degeneration in at least one region; and 3) the absence of electrophysiological and pathological evidence of other disease processes that might explain the signs of LMN and/or UMN degeneration, and neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs. Therefore the patients registered in this system satisfy definite, probable or possible ALS based on the revised El Escorial Criteria [15] for the diagnosis of ALS.

The data collection system was developed in 32 of 47 prefectures in Japan. In proportion to the total population, 63% of total registered patients in Japan were integrated into the computerized database. The data were comprised of initial registration form and renewal registration form. When a patient was diagnosed as ALS, the initial registration form was used to apply for the system, and the renewal registration form was used in the following year. However, the information on the patients initially registered before 2003 was comprised of data from only renewal registration.

After 2003, 3694 ALS patients were newly registered in the system. Records were eliminated from the analysis if information was missing for age at onset and age at registration. Ninety-four patients were also excluded who had a family history of motor neuron disease or an abnormality of genes related to neurodegenerative disease such as the SOD1 mutation. The inclusion age range was above 20 years at onset. After these data clearing, the data from a total of 3428 patients were available. In order to analyze the age at onset, initial symptoms and related clinical features, we used this data set.

In a single year, 2005, 4546 ALS patients were registered using the initial registration form or renewal registration form. The number included those initially registered before 2003. To describe the cross-sectional overview of the medical and social conditions of ALS patients in Japan, we used this data set. After the data described above were excluded, the data from 4202 patients were used.

From 2003 to 2006, 2440 ALS patients with TPPV were registered at least once, mostly using the renewal registration form. The number included those initially registered before 2003. To describe the conditions of ALS patients with TPPV, we analyzed this data set. After the data cleaning, the data from 2128 patients with TPPV were used.

All of the patients provided written informed consent for the research use of the data, and the anonymity of the data was strictly secured. We implemented the guidelines for research use of the data from the nationwide registration system of intractable diseases and the ethics guidelines for clinical studies endorsed by the Japanese government. The research project was approved by the Ministry of Health, Labor and Welfare, Japan, and by the ethics committee of Nagoya University Graduate School of Medicine.

2.1. Assessment of clinical features

Age at onset was considered as the time of the patient's initial awareness of weakness. As for the initial symptoms, six symptoms including dysarthria, dysphasia, respiratory disturbance, weakness of neck, weakness of upper extremities and weakness of lower extremities were noted. In most cases, one symptom was assessed as an initial symptom, however, two or more symptoms may be recorded. The activities of daily living and clinical symptoms were assessed by 6 items from the 12 items of ALSFRS-R (Speech, Swallowing, Handwriting, Dressing and Hygiene, Walking and Dyspnea). The Japanese version of ALSFRS-R was validated previously for ALS, showing that the assessment values are highly equivalent among well-trained neurologists, general physicians and nurses, and that intra-rater assessment values are also highly equivalent [16]. Intra-rater and inter-rater reliability of each item of the Japanese version of ALSFRS-R were also validated. The presence of oculomotor disturbance was assessed through a bedside neurological examination.

2.2. Data analysis

All variables were summarized using descriptive statistics, including mean, standard deviation (S.D.), and percentages. Correlations

Table 1
Clinical features of patients newly registered from 2003 to 2006 (n=3428)

Age at onset (years, mean±S.D.)	65.4±10.7
Male/female (%)	57.8/42.2
Duration from disease onset to registration (years, mean±S.D.)	1.7±2.2
Symptoms at registration (%)	
Dysarthria	64.2
Dysphagia	57.8
Weakness of neck	70.0
Respiratory distress	34.2
Weakness of upper extremities	86.6
Weakness of lower extremities	76.2
Initial symptoms (%)	
Dysarthria	36.3
Dysphagia	21.1
Weakness of neck	7.1
Respiratory disturbance	6.3
Weakness of upper extremities	48.1
Proximal dominant	26.1
Distal dominant	50.8
Diffuse	23.0
Weakness of lower extremities	34.1
Proximal dominant	19.7
Distal dominant	42.6
Diffuse	37.8

Table 2
Cross-sectional living conditions of patients registered in 2005 (n=4202)

Living condition	Frequency (%)
At work or school	6.7
Household work	6.5
Under home care	58.2[a]
In hospital	27.5[a]
In nursing-care facility	2.4

[a] 1.2% of patients overlap.

between age at onset and duration from disease onset to invasive procedures were analyzed using Pearson's correlation coefficient, and the cumulative incident curves of two age groups were assessed by the log-rank test. Difference of frequencies of symptoms between two age groups was assessed by the chi-square test. p-values <0.05 were considered to be statistically significant. Calculations were performed using the statistical software package SPSS 15.0J for Windows (SPSS Japan Inc., Tokyo Japan).

3. Results

3.1. Clinical features of sporadic ALS patients

The mean age at onset was 65.4±10.7 years, the male to female ratio was 1.37:1, and the mean duration from disease onset to registration was 1.5±1.4 years. The initial symptom was dysarthria in 36.3%, dysphagia in 21.1%, weakness of neck in 7.1%, respiratory disturbance in 6.3%, weakness of the upper extremities in 48.1%, weakness of lower extremities in 34.1%, when allowing overlapping descriptions (Table 1). When we analyzed these demographic clinical features between male and female patient groups, age at onset was slightly higher in the female patients. The proportion of the patients with bulbar symptom onset was higher in the female patients, whereas, the proportion of the patients with weakness of upper extremities was higher in the male patients (Supplemental Table 1).

The cross-sectional state of living conditions of ALS patients in Japan in 2005 is shown in Table 2. The proportion of the patients at work or school was 6.7%, 6.5% engaged in household work, 58.2% under home care, 27.5% in hospital and 2.4% in a nursing-care facility. The state of nutrition and respiratory support is shown in Table 3. The frequency of patients with a gastrostomy tube was 28.7%, and 7.8% were using a nasogastric tube. NIPPV was used by 7.2% of the patients, and 29.3% were under TPPV. The clinical profiles of the patients with TPPV were shown in Table 4. Mean duration from introduction of TPPV was 3.7 years, and 42.2% of the patients with TPPV were living under home care.

3.2. Age at onset influences progression of disease assessed by duration from onset to introduction of TPPV

The mean interval between the onset of disease and the introduction of TPPV was 3.0 years. Intervals from the disease onset to the introduction of TPPV became shorter as the age at onset advanced (Fig. 1A). There was a significant correlation between the

Table 3
Nutritional and respiratory support of patients registered in 2005 (n=4202)

Nutritional and respiratory support	Frequency (%)
Tube feeding	
Gastrostomy tube	28.7
Nasogastric tube	7.8
NIPPV [a]	
Intermittent use	2.0
All-night use	2.6
All-day use	2.6
TPPV [b]	29.3

[a] Non-invasive positive pressure ventilation.
[b] Tracheostomy positive pressure ventilation.

Table 4
Clinical profiles of patients with TPPV (n=2128)

Male/female (%)	59.9/40.1
Age at onset (years, mean±SD)	59.8±11.7
Duration of disease (years, mean±SD)	6.7±5.0
Duration from disease onset to introduction of TPPV	3.0±3.2
Duration from TPPV introduction	3.7±3.5
Living conditions	
Under home care (%)	42.2[a]
In hospital (%)	57.4[a]
In nursing-care facility (%)	2.1

[a] 1.8% of patients overlap.

age at onset and the interval from disease onset to introduction of tube feeding or TPPV, when analyzed using Pearson's correlation coefficient (r=−0.39 p<0.001). Since 65 years was the mean age of onset, we assessed the cumulative frequency of TPPV in subgroups of patients with an age at onset of 65 years or more and less than 65 years, showing that the duration from onset to introduction of TPPV was significantly shorter in patients with an onset age of 65 years or older (p<0.001) (Fig. 1B). The age at onset influences the progression from onset to the advanced stage assessed by the introduction of TPPV.

3.3. Appearance of ophthalmoplegia under TPPV influenced by age at onset

In the patients with long-standing TPPV, rare symptoms such as ophthalmoplegia were frequently observed. Ophthalmoplegia, which is particularly well assessed by bedside examination, was seen in only

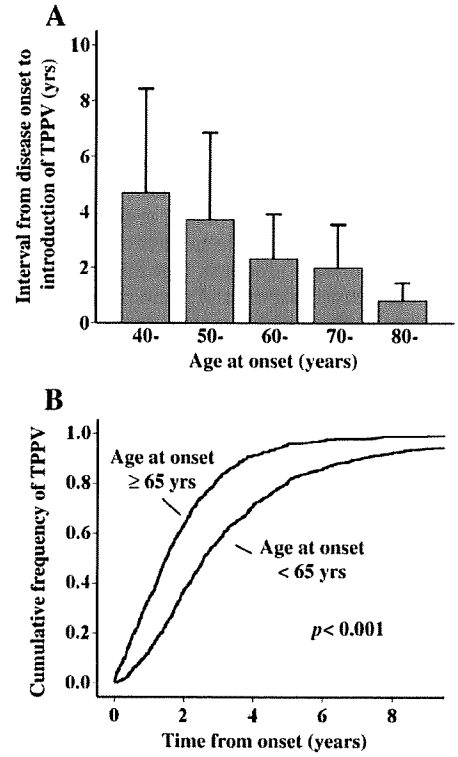

Fig. 1. Relationship between age at onset and introduction of tube feeding and TPPV. Interval from disease onset to introduction of TPPV (A) is shown. An older age at onset strongly correlates to shorter intervals from onset to TPPV. Cumulative frequencies of patients with TPPV in the patient population with an onset age older or younger than 65 years are shown (B). Cumulative curves for patients with an onset age of 65 years or more show significantly shorter intervals between disease onset and introduction of TPPV than those with an onset age of under 65 years of age, suggesting that age at onset markedly influences the time from onset to introduction of TPPV. n=2128.

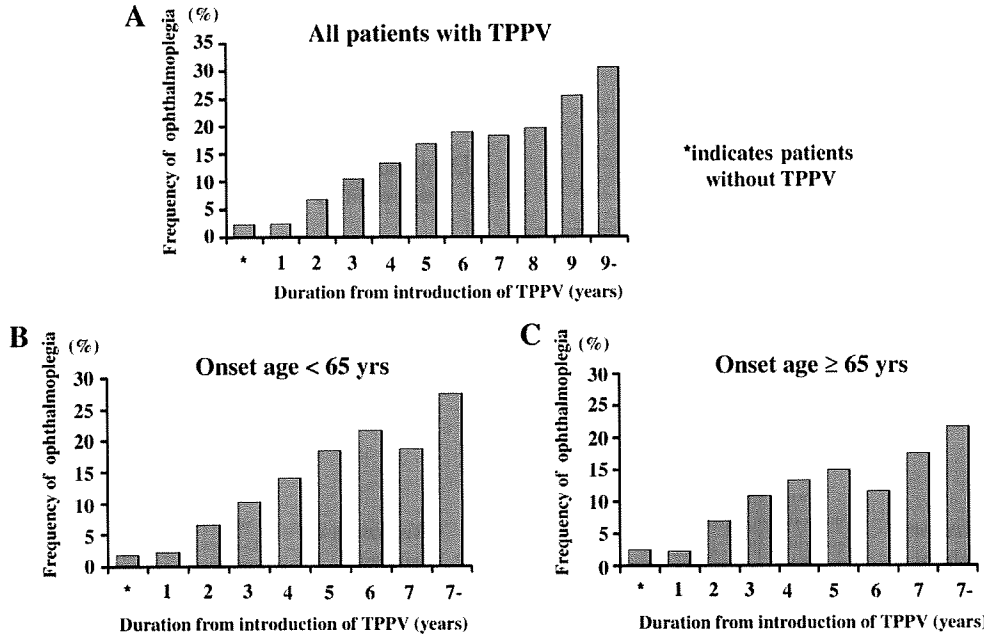

Fig. 2. Frequency of ophthalmoplegia in patients under TPPV, in terms of duration of TPPV and the influence of onset age on its appearance. Ophthalmoplegia rarely occurs in patients without TPPV (*), while its occurrence gradually increases with advanced duration of TPPV (A). Following 9 years of TPPV, almost 30% of patients show ophthalmoplegia. Frequencies of ophthalmoplegia in the patient population with onset age older or younger than 65 years are shown in B and C. Ophthalmoplegia is less frequent in patients with an age at onset of 65 years or older (C). The total frequency of ophthalmoplegia in the patients with onset age older than 65 years or younger than 65 years is 8.3% and 15.1%, respectively. A significant difference exists between them by the chi-square test ($p<0.001$). $n=2128$.

2.0% of the patients without TPPV. The frequency of ophthalmoplegia was increased with the advanced duration of TPPV (Fig. 2A). However, ophthalmoplegia was observed in 30% of patients under TPPV for more than 9 years.

The appearance of ophthalmoplegia under long-standing TPPV is also influenced by the age at onset (Fig. 2B,C). The patients with an age at onset under 65 years showed a higher frequency of appearance of oculomotor symptoms than those with an age at onset over 65 years (Fig. 2B,C). The total frequency of ophthalmoplegia in the patients under TPPV with an onset age of older than 65 years or younger than 65 years was 8.3% and 15.1%, respectively. A significant difference was found between them by the chi-square test ($p<0.001$). These observations suggest that a younger age at onset advances the appearance of ophthalmoplegia compared to patients with an older age at onset. The average time from onset to introduction of TPPV was, however, 1.86± 1.70 years in the patients with an onset age over 65 years, and 3.60± 3.72 years in those with an onset age of younger than 65. This difference influenced the appearance rate of ophthalmoplegia.

3.4. Age at onset influences the frequency of initial symptoms

We analyzed the relationships between the age at onset and the initial symptoms. Dysarthria and dysphagia as the initial symptoms were markedly increased in patients with an advanced age at onset

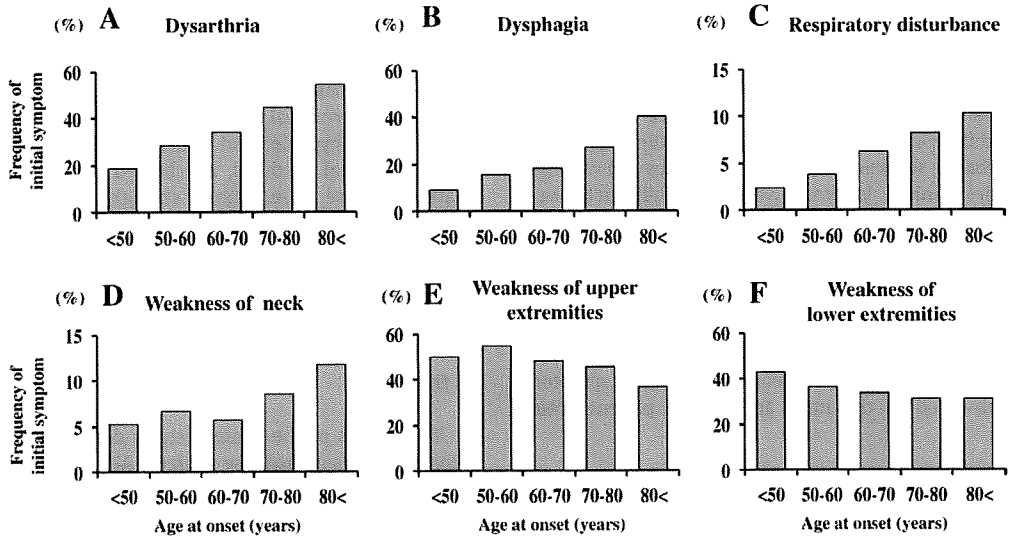

Fig. 3. Age at onset and frequency of initial symptoms. Dysarthria (A), dysphagia (B), respiratory disturbance (C) and weakness of neck (D) are increased in frequency as an initial symptom as the age at onset increases. In contrast, weakness of the upper extremities (E) or lower extremities (F) decreased as the onset age increases. $n=3428$.

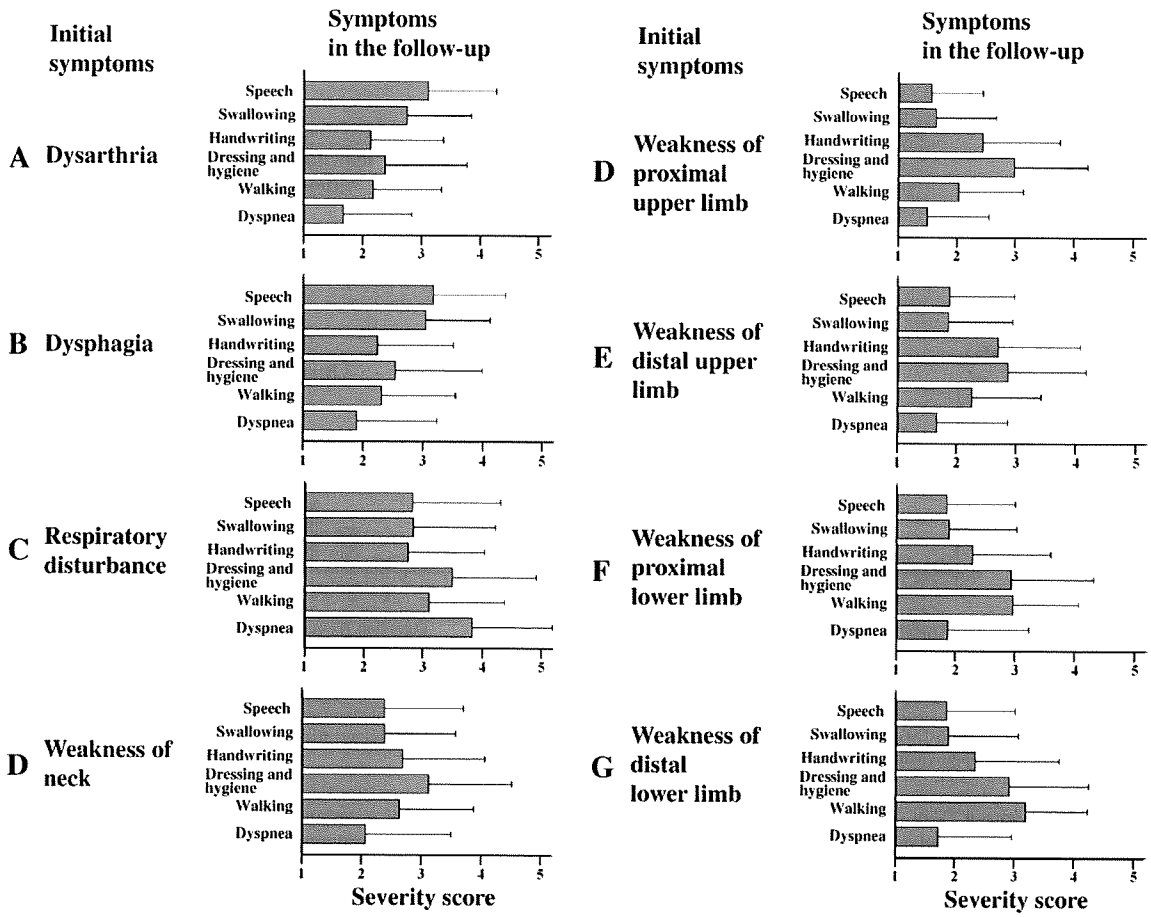

Fig. 4. Relationship between initial symptoms and symptoms at the follow-up stage. Severity scores of Speech, Swallowing, Handwriting, Dressing and Hygiene, Walking and Dyspnea are shown as subscales of ALSFRS-R. The score of "5" represents the most severe state, and "1" represents the absence of the symptom. Initial symptoms remain the most prominent or related symptoms even in the follow-up stage for 1.7±2.2 years from onset, suggesting that initial symptoms significantly determine the prominent features of symptoms throughout the disease course. $n=3428$.

(Fig. 3A,B). On the other hand, weakness in the upper or lower limbs as an initial symptom was seen more frequently in patients with a younger age at onset, and these frequencies gradually decreased with increasing age at onset. As for the respiratory disturbance and dropping head due to weakness of the neck muscles, the frequencies increased gradually with increasing age at onset. When we divided the patients between those with an onset age of older than 65 years and those younger than 65 years and analyzed the data with the chi-square test, the differences in frequencies of dysarthria, dysphagia, respiratory disturbance, weakness of upper extremities and weakness of lower extremities as initial symptoms were also significant between those groups ($p<0.001$, $p<0.001$, $p<0.001$, $p=0.001$, $p=0.019$, respectively). The difference in the frequency of neck weakness was not significant ($p=0.07$), although the tendency was apparent, and may be due to the small number of patients with neck weakness as an initial symptom. These observations suggest that age at onset is a determining factor of the features of the initial symptoms. Correlations between age at onset and the frequency of initial symptoms were similarly observed in the male and female patient groups (Supple. Fig. 1).

3.5. Initial symptoms determine major clinical features in follow-up stage

We examined the relationship between the initial symptoms and the symptoms assessed by 6 items of ALSFRS-R at examination at 1.7± 2.2 years after the onset (Fig. 4). At the follow-up stage, the patients who showed a bulbar symptom as an initial symptom showed speech or swallowing disturbance as a major symptom in the follow-up stage. Patients that showed respiratory disturbance as an initial symptom also showed dyspnea as the most prominent disturbance; patients with weakness of distal upper limb muscles showed the most prominent disturbance in handwriting and dressing; patients with weakness of proximal upper limbs showed prominent disturbance in dressing and hygiene; and patients with weakness of lower limbs, either proximal or distal, all showed a prominent disturbance in walking. These observations strongly suggested that the initial symptoms remained the most prominent or related symptoms even in the follow-up stage, and support the view that the initial symptoms determine the clinical features of the individual patient even in the follow-up stage. A similar tendency was observed in the male and female patient groups (Supple. Fig. 2).

4. Discussion

The results of the present study demonstrate the characteristic clinical profiles of Japanese sporadic ALS patients. A very high rate of Japanese ALS patients (29.3%) were under TPPV compared to patients in North America or Europe [10,11,17,18] which are 2.1–5.4%, respectively. The frequency of patients showing rare symptoms such as ophthalmoplegia increased with disease progression, particularly under long-standing TPPV.

A striking observation in the present study is that the age at onset greatly influences the wide-ranging clinical features, including the initial symptoms, progression to the endstage assessed by introduction of TPPV, and the frequency of rare symptom in the long-standing course. A higher incidence of bulbar involvement in patients with an older age at onset has been reported in some previous studies [19–23]. We extended these observations in that almost all of the initial symptoms, such as dysphagia, dysarthria, upper or lower limb weakness, respiratory failure and head dropping are strongly influenced by the age at onset. This observation was also confirmed in the subpopulation of male and female patients. In addition, since the initial symptoms also determine the prominent clinical phenotypes in the follow-up stage as demonstrated in this study, age at onset may influence not only the initial symptoms, but also the entire clinical phenotypes of sporadic ALS. The underlying mechanism for the onset age influence on the initial manifestation of the symptoms is unknown. Furthermore, we do not know the mechanism by which patients with a younger age at onset tend to show a higher frequency of rare symptoms. Further study is needed to resolve these issues, although one may speculate that subpopulations of the motor neurons may be differentially vulnerable to the aging process. In several sporadic neurodegenerative diseases, age at onset has been suggested to be an influencing factor for the spatial development of neural involvement, and, thus, for the features of clinical manifestations [24]. In Parkinson's disease, for instance, patients with an older age at onset have been suggested to have a tendency to show a higher cognitive dysfunction and autonomic dysfunction [25–27], whereas, those with a younger age at onset have an increased tendency toward dystonia and a diurnal fluctuation of symptoms [28,29]. Taking these observations together with our findings on ALS, age at onset may be a more important factor modifying clinical manifestations in sporadic neurodegenerative diseases than previously thought.

Age at onset also influenced the interval from the onset to the time of introduction of TPPV. Reserved respiratory function is known to decrease with advancing age [19]. Therefore, the short interval between the onset and the introduction of TPPV may be explained by the smaller reserved respiratory capacity in elderly patients. Indeed, serial examinations of the respiratory function in elderly patients start at a lower vital capacity and reach a critical point more quickly than younger patients [19,30]. It is congruent with the fact shown in the previous reports [1,3,5,6,22], that younger ALS patients survive longer than older patients.

Therefore, in taking into account the age at onset, initial symptoms, occurrence of rare symptoms and progression, the age at onset greatly affects the clinical profiles of sporadic ALS patients. In addition, the onset age-related initial symptoms are important to estimate the patient's prognosis as well as the design of clinical trials [31].

A high proportion of ALS patients in Japan are under TPPV compared to patients in other countries, possibly for social, cultural and economic reasons [13,17,18]. The presence of a subgroup of patients extending involvement to other systems beyond motor neurons, such as oculomotor, autonomic, sensory and higher functional systems, has been described in Japanese ALS patients under long-term TPPV treatment [32–36]. Pathologically, these patients show an extensive involvement of the tegmentum of the brainstem, substantia nigra, Clarke's dorsal nuclei and spinocerebellar tract, and frequent involvement of the thalamus and globus pallidus. Our present observations have confirmed these reports on sporadic Japanese ALS patients, particularly those with long-standing TPPV, and demonstrated that these subpopulations with a rare extension of involvements include almost 30% of the patients with 9 years or more under TPPV, particularly those assessed for oculomotor system involvement. However, further studies are needed to determine whether all the patients would eventually show an extended involvement beyond the motor system or whether these patients with an extended form are restricted to a given subpopulation. This is an important issue to determine the natural history of sporadic ALS. Since European and American ALS patients are not generally maintained on TPPV treatment for a longer period as Japanese patients, extended involvement is very rarely observed in Europe or North America.

In summary, we have presented the clinical profiles of sporadic Japanese ALS patients based on a large-scale sample. As demonstrated, age at onset may be a remarkable factor influencing wide-ranging clinical profiles including the progression and prognosis. We should take account of this observation in cohort studies or clinical trials.

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Appendix A

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Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jns.2008.09.024.

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