けている．そのため運動ニューロンにおいてもグルタミン酸受容体が高密度で発現しており[4]，グルタミン酸による興奮が過剰になるとCa^{2+}などのイオン透過性亢進が引き起こされ，細胞内環境の変化を補償する機能を越えてしまい，その結果として細胞死のカスケードが働く，というのが興奮性神経細胞死のメカニズムである．これは，主に虚血や低血糖，外傷，てんかん重積などの急性の神経細胞死に働くと考えられていた[5]．一方で近年，培養細胞系，*in vivo*動物実験系で急性には神経細胞死を引き起こさない濃度でも受容体が長期間持続的に興奮することで遅発性の神経細胞死が起こることが次々と明らかにされ，特にALSでグルタミン酸受容体を介した経路が関与している可能性が注目されるようになった[6,7]．

動物実験では器官培養脊髄の前角運動ニューロンにおいて培養液中にグルタミン酸トランスポーターの阻害剤を加えると変性が起こり[8]，長期間持続的にトランスポーターをコードするmRNAのアンチセンスmRNAを投与し，トランスポータータンパクの発現を抑えるとラット脊髄運動ニューロンに変性が生じた．また，ラット脊髄クモ膜下腔にグルタミン酸トランスポーター阻害剤であるTHAを投与することにより，AMPA受容体を介した遅発性の神経細胞死が後角ニューロンに生ずる[9]．これらの結果から，グルタミン酸トランスポーターの異常によりシナプス間隙のグルタミン酸濃度が上昇すると脊髄運動ニューロンが障害されることが示された．この神経細胞死はAMPA受容体アンタゴニストにより回避されるのでAMPA受容体の持続的興奮が関与していることが示されている．さらに，プライマリーカルチャーでは，脊髄前角ニューロンは後角ニューロンに比べ，AMPA受容体アゴニストに対する毒性に脆弱であること[10]，AMPA受容体アゴニストを長時間持続的にラット脊髄クモ膜下腔に投与すると後角脊髄ニューロンに遅発性の神経細胞死を起こし[11]，特にカイニン酸の4～8週間の持続投与では運動ニューロンが選択的に変性することが*in vivo*実験で示され[12]，AMPA受容体の持続的興奮により運動ニューロンに遅発性の神経細胞死が起きることが様々な実験系で示された．これらはAMPA受容体を介する神経細胞死がALSの神経細胞死に働いていることを示唆するものである[2,3]．

B. 神経細胞死とAMPA受容体

グルタミン酸受容体は大きくイオンチャネル型と代謝調節型に分類される．そしてイオンチャネル型はさらにNMDA受容体，カイニン酸受容体，AMPA受容体に分けられる．NMDA受容体が急性の神経細胞死に関与するのに対して特に速いシナプス伝達にかかわるAMPA受容体は，ニューロンの遅発性の細胞死に関与し，運動ニューロンは，特に後者の興奮性細胞死に脆弱であることが知られている．その分子メカニズムとして細胞死に先立つ過剰なCa^{2+}流入による細胞内Ca^{2+}濃度の持続的上昇が培養ニューロンで明らかにされ，それに引き続くCa^{2+}依存性プロテアーゼの活性化，ミトコンドリア障害，NOS産生などによるカスケードが細胞死を引き起こすことが様々な実験系により明らかにされた[13]．神経細胞内Ca^{2+}濃度上昇の機構には，1）NMDA受容体の活性化によるチャネルからのCa^{2+}流入，2）Ca^{2+}透過性AMPA受容体の活性化，3）代謝型グルタミン酸受容体などの興奮によるIP3産生を介する小胞体からのCa^{2+}動員，4）膜の脱分極による膜電位依存性Ca^{2+}チャネルの開口などのメカニズムが知られている[14]．最近は電位非依存性カチオン透過性チャネルの関与も示唆されている（例：transient receptor potential，以下TRP）[15]．なぜ神経細胞死にAMPA受容体のCa^{2+}透過性の関与が大きいのか，についてはまだ不明な点が多い

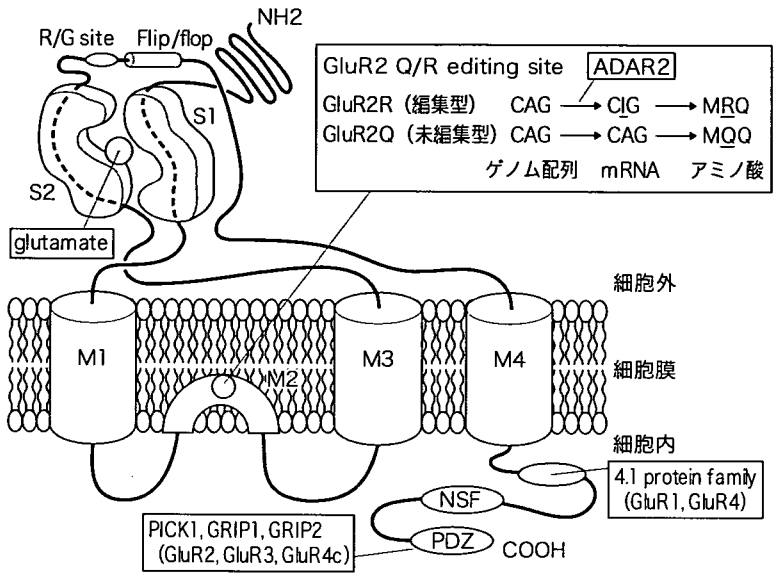

図1 AMPA受容体の構造（文献2,3,16-20より改変）

AMPA受容体は4種類のサブユニットGluR1～GluR4から構成される4量体からなる．M1～M4は膜ドメイン．S1とS2は仮想的グルタミン酸結合部位．各サブユニットにはそれぞれ選択的スプライシングにより異なるアミノ酸配列をもったflip型とflop型という2つのタイプがあり，発生時期や脳の部位で異なっている．GluR2～4にはR/G部位があり，RNA編集によりアルギニン（R）からグリシン（G）へ置換する．この部位は受容体脱感作を修飾する．さらにGluR2の多様性が生じるメカニズムとしてM2に存在するQ/R編集部位があり，翻訳過程でCAGまたはCAA（グルタミン（Q））がCGGまたはCGA（アルギニン（R））になる．そのため，サブユニットの組み合わせの違いが機能的な多様性をもたらすと推測される．細胞内C末端領域にはPKA，PKC，CaMKIIによるリン酸化部位やGRIP，PICK，SAP97などのPDZタンパク質結合部位が局在する．この領域はPDZドメインを介してGRIPなどpostsynaptic density（PSD）タンパクと結合し，シナプスでのAMPA受容体の安定化などにかかわっている．また，AMPA受容体はTARPタンパク（本文参照），stargazinタンパク（VDCC γ2），VDCC γ3-8と膜表面で共在することが知られており，これらのタンパクがチャネル活性とかかわっていることがわかっている．

PDZ: Postsynaptic density-95/Discs large/Zona occuludens-1,
PKA: protein kinase A, PKC: protein kinase A,
CaMKII: Ca^{2+}/ calmodulin-dependent protein kinase phosphates II, GRIP1: glutamate receptor-interacting protein type 1, GRIP2: glutamate receptor-interacting protein type 2,
PICK: protein that interacts with C kinase, SAP97: synapse-associated protein 97,
NSF: N-ethylmaleamide sensitive factor, PSD: postsynapitic density,
VDCC: voltage-dependent Ca^{2+} channel
図中のCIGは，リボソームでIはグアノシン（G）と同等であると見なされるため，CIGというコドンはCGGと見なされRとして翻訳される（本文参照）．

が，どのようにCa^{2+}透過性が制御されているかは少しずつ解明されている．

AMPA受容体は，4種のサブユニット（GluR1-GluR4）の単独または様々な組み合わせからなる4量体である．各サブユニットは共通構造をもち，相互に約70%のアミノ酸配列の相同性をもち，細胞外のN端，膜ドメイン（M1～M4），細胞内のC端からなる（図1）[2,3,16-20]．AMPA受容体

のCa^{2+}透過性を決定する因子には，1）GluR2サブユニット，2）GluR2サブユニットのRNA編集（特にQ/R部位），3）flip/flop splicing variantやR/G部位の編集率などチャネルの開口を編集するドメインがあり，細胞全体としては[4]細胞表面のAMPA受容体密度もCa^{2+}流入量を決定する大きな因子となる．しかし，これらの因子のすべてが細胞死に直接関連するわけではなく，AMPA受容体仮説には後述するように1)と2)のかかわりが大きい．

第一にチャネルのCa^{2+}透過性決定に重要な役割をはたしているのはGluR2サブユニットである．AMPA受容体を構成する4つのサブユニットのうちGluR2を含む受容体は，Ca^{2+}透過性が低く，GluR2を含まないGluR1，3，4のサブユニットだけで構成された受容体は，高いCa^{2+}透過性を示す[21-23]．

つまりAMPA受容体のCa^{2+}透過性は，GluR2の有無により決定される．たとえば，ラット小脳プルキニエ細胞や海馬錐体細胞などでは，他のサブユニットに比べGluR2が多く発現し，AMPA受容体のCa^{2+}透過性は低く[24]，海馬のバスケット細胞，新皮質の非錐体細胞，小脳のBergmannグリア細胞などではGluR2サブユニットがほとんど発現していないため，Ca^{2+}透過性は高い[25]ことが知られている．

第二にAMPA受容体の各サブユニットのM2にあるQ/R部位がCa^{2+}透過性を制御している．Q/R部位がCa^{2+}透過性決定に重要なのはチャネル・ポアに面しており，陽電化のRがCa^{2+}を弾くのに対して電気的に中性のQではこの作用が弱いためであると考えられている．同部位はGluR2以外ではグルタミン（Q）であるのに対して，GluR2だけはアルギニン（R）である（図1）．しかしゲノムレベルでは，GluR2も他のサブユニット同様にQをコードしている．どうしてRになるのかというと，RNA編集という現象が起こるためである．つまり，DNAからRNAへ転写後，mRNAになる前に，adenosine deaminase acting on RNA type 2（以下ADAR2）とよばれる編集酵素により，アデノシン（A）からイノシン（I）へとRNA編集が起こることで塩基置換され，リボソームでIはグアノシン（G）と同等であると見なされるため，CIGというコドンはCGGと見なされRとして翻訳される[26]．未編集型GluR2（Q）は他のサブユニット同様AMPA受容体のCa^{2+}透過性を制御できないので，編集型GluR2（R）を含んだAMPA受容体の割合が減少する，あるいは未編集型GluR2（Q）を含んだAMPA受容体の割合が増加すると細胞内へのCa^{2+}流入が高まる[27]．RNA編集は，GluR2 Q/R部位以外にもカイニン酸受容体サブユニットであるGluR5，GluR6のQ/R部位やGluR2，GluR3，GluR4サブユニットのR/G部位，Kv1.1 I/V部位，$5HT_{2c}$ A～E部位ではRNA編集の有無によりチャネル特性に変化が生じ，ADAR2のself-editingではスプライシングサイトの変化によるフレームシフトにより，酵素活性が変化する[28]など様々なRNAのそれも複数の部位で生じているが，その編集率は一定せず様々である．ところが，GluR2のQ/R部位は，胎生期から成熟期に至るまでほぼ100%編集されている[29]という点で特異的であり，他には見いだされていない．

しかし，GluR2のノックアウトマウスでは細胞死が生じず[30]，一方でRNA編集を阻止したmutant mouseはGluR2 Q/R部位が0.1%以下に低下し，生後20日以内に痙攣重積により死亡する[31]ことなどからGluR2のRNA編集にはQ/R部位の電荷状態の制御以外にも，AMPA受容体の機能を修飾する作用があると考えられ，生存を左右するほど生物学的にもきわめて重要な意味をもっていると推測される．

その修飾作用の一つが，ニューロン表面のAMPA受容体密度，サブユニット会合効率への

関与である．GregerらはQ/R部位がQかRであるかによってサブユニットの会合確率が変わり，特に4量体形成において主な要因となること，すなわち，未編集型GluR2（Q）は編集型GluR2（R）よりも効率的に機能的AMPA受容体を形成しやすいことを示した[32]．さらにQ/R部位のアミノ酸残基の違いによりtrafficking効率が異なり，Q型（GluR1, 3, 4, 未編集GluR2（Q））はR型（編集型GluR2（R））に比し効率が高いこと，すなわち未編集型GluR2（Q）が存在する場合には編集型GluR2（R）が小胞体から輸送されにくいのに対して，GluR2（Q）を含むサブユニット複合体は，効率よく膜表面にtraffickingされることを示した[33]．以上のようにQ/R部位がQであるかRであるかによってサブユニットの会合確率およびtrafficking効率が異なり，結果的にGluR2の細胞膜表面へのtrafficking効率は，編集型GluR2（R）より未編集型GluR2（Q）のほうがはるかに高くなる．すなわち，GluR2ノックアウトマウスには細胞死が起こらないのに，RNA編集異常マウスで痙攣重積が起こるのは，RNA編集の障害の方が細胞表面のCa^{2+}透過性AMPA受容体密度が高く，細胞内Ca^{2+}濃度の上昇もより大きいので神経細胞死が起こると考えられる．培養細胞では，未編集型GluR2発現させても，traffickingを阻止すると神経細胞死も阻止される[34]．

C. AMPA受容体サブユニット発現とALSの運動ニューロン死

これらの結果を踏まえ，神経細胞死に関連する分子変化であるGluR2の減少（Ca^{2+}透過性AMPA受容体の割合の増加）ないしGluR2 Q/R部位の編集率低下（Ca^{2+}透過性AMPA受容体の実質的増加）の有無をALSの運動ニューロンで検討するためにKwakらはlaser microdissectorを用いて凍結剖検組織から単一神経細胞を切り出し，孤発性ALS脊髄運動ニューロンの単一神経細胞レベルの検討において，GluR2 mRNA発現量に有意な減少がないこと[35]，および脊髄前角組織レベルで，すでに報告していた[36]部位選択的・疾患特異的なGluR2 Q/R部位の編集率低下を確認した[1]．図2に示すように，正常対照群の運動ニューロンでは，全例GluR2 Q/R部位は100% RNA編集されていたが，ALS群では0～100%とばらつき，平均値は38～75%と低下していた．ALS群における小脳プルキンエ細胞の編集率は，正常対照群と同様にほぼ100%に保たれていた．また，他の神経変性疾患の同細胞を検索したが，編集率は正常対照と同様のレベルによく保たれていた．さらに症例数を増やし，孤発性ALSと診断された症例で，古典型，PBP，ALS-D，好塩基性封入体が出現する若年発症例[37]について編集率を調べたところ臨床像の異なるこれらのALSでも編集率は低下しており，共通の分子異常が発症のメカニズムにあることが推測される[38]．一方でSOD1関連性家族性ALS（ALS1）モデルラットやSBMA（球脊髄性筋萎縮症）の運動ニューロンでは同部位の編集率はコントロールと同様であり[39]，これらの疾患の運動ニューロンでは孤発性ALSとは異なる細胞死のメカニズムが働いていると考えられる．一方で，変異*SOD1*トランスジェニックマウスでは，AMPA受容体を介した神経細胞死が働いていることが，GluR2欠損マウスとの交配による興奮毒性の増強[40]やCa^{2+}を透過するQ/R部位を人工的なGluR2〔GluR-B（N），N（アスパラギン）〕を導入した変異マウスと変異*SOD1*遺伝子のdouble transgenicマウスにおける神経細胞死の促進[41]から示されている．ALS1でGluR2のRNA編集が正常だとすると，GluR2の欠乏によるAMPA受容体のCa^{2+}透過性亢進が予想されるが，GluR2の過剰発現により生存期間が延長することを示した報告[42]，GluR3の発現量が増加しているとする

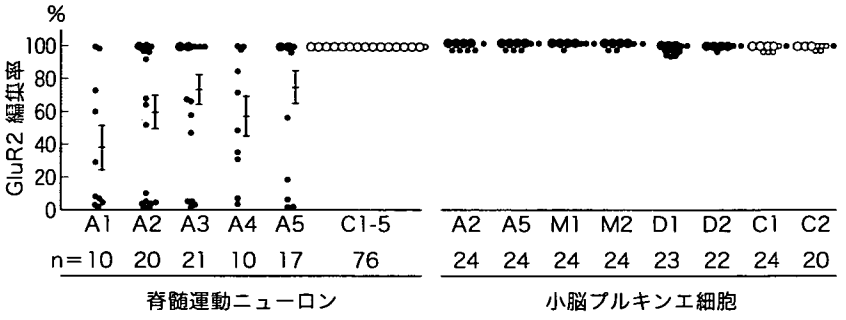

図2　単一神経細胞におけるGluR2 Q/R部位RNA編集率（文献1より改変）
各点（大きな点は5細胞，小さな点は1細胞）は，ALS群5例（A1-A5），コントロール群5例（C1-C5）の単一脊髄運動ニューロンにおけるGluR2 Q/R部位のRNA編集率と，ALS群2例（A2，A5），multiple system atrophy（以下MSA，多系統萎縮症）群2例（M1，M2），dentatorubral-pallidoluysian atrophy（以下DRPLA，歯状核赤核淡蒼球ルイ体萎縮症）群2例（D1，D2），コントロール群2例（C1，C2）の単一小脳プルキンエ細胞の編集率を表している．平均値± 標準誤差と解析した細胞数（n）も示した．運動ニューロンにおける正常コントロール76個の内訳は，C1; 28，C2; 12，C3; 13，C4; 12，C5; 11である．運動ニューロンでは，正常コントロール群のすべての細胞において，例外なく編集率は100%であった．これに対して，ALS群では，解析した5ケースすべてにおいて，編集率は運動ニューロンごとに0%から100%まで大きくばらつき，平均値も正常コントロール群と比較し，有意に低下していた（Mann-Whitney U test，$p<0.001$）．一方，小脳プルキンエ細胞における編集率については，ALS群，MSA群，DRPLA群とコントロール群の間には有意差はない（Mann-Whitney U-test，$p>0.05$）．

報告[43,44]は，この予測を支持する．特に，GluR3の発現量増加は，我々がカイニン酸を長期髄注することにより作成したALSのモデルラットにもみられる分子変化であり[45]，変異SOD1トランスジェニックマウス，家族性ALS1ではAMPA受容体の持続的刺激により運動ニューロンの興奮性が高まった結果，相対的にGluR2の割合が下がることでAMPA受容体のCa^{2+}透過性が亢進し，細胞死に至るカスケードにつながることが予想される．このように，ALS1と，痴呆を伴うALSを含む孤発性ALSとでは，神経細胞死を引き起こす分子メカニズムが異なることは，ALS，前頭側頭型痴呆（FTLD）の細胞内封入体に特異的に集積することが示されているTDP-43が，ALS1には見いだされていない[46,47]ことからきわめて興味深い．他方，アンドロゲン受容体のCAGリピートが伸長しているSBMAでは，同じポリグルタミン病であるHuntington病モデルマウスでの検討から[48-51]，AMPA受容体を介した神経細胞死は働いていないと考えられる．このように運動ニューロン疾患の神経細胞死には図3に示すように，異なる複数の分子メカニズムが独立に働き，ALSにはAMPA受容体を介する運動ニューロン死が働いているものの単一の分子メカニズムではないことが推測される[52]．

以上から，孤発性ALS脊髄運動ニューロンで認められたRNA編集異常は，細胞選択的かつ疾患特異的な分子変化であり，神経細胞死に直接かかわっている可能性が高いと考えられる．このような選択性・特異性を生む機序としては，脊髄運動ニューロンのAMPA受容体総mRNA発現量およびGluR2サブユニットのAMPA受容体サブユ

ニット全体に占める比率が，他のニューロンに比べて，低く[35,53]，もともとCa^{2+}透過性AMPA受容体の割合が多いためにRNA編集低下の影響を受けやすいことがあげられる．また，これまでのADAR2ノックアウトマウスの研究から，ADAR2活低下がGluR2 Q/R部位の編集異常を通じて神経細胞死の直接原因になり得ること[54]が明らかにされている．ADAR2活性を規定する因子の一つはmRNA発現レベルであり[55,56]，孤発性ALS前角組織では正常対照に比し，ADAR2mRNA発現量が低く[16]，ALS脊髄運動ニューロンではADAR2の酵素活性が低下していることがGluR2 Q/R部位RNA編集異常の原因と考えた．この仮説を証明するために，私たちのグループはADAR2の解析を進めている．

D. ALSの治療に向けて

前述のように孤発性ALSの疾患病態と直接かかわっていると考えられるAMPA受容体関連の分子異常が見つかり，発症メカニズムに基づいた分子標的治療法を開発できる可能性が高まってきた．運動ニューロン選択的にGluR2 Q/R部位のRNA編集を回復できれば，ALSの治療へとつながるものと考えられる．我々は前述の仮説に合致する事実を次々と明らかにしているが，なぜALS

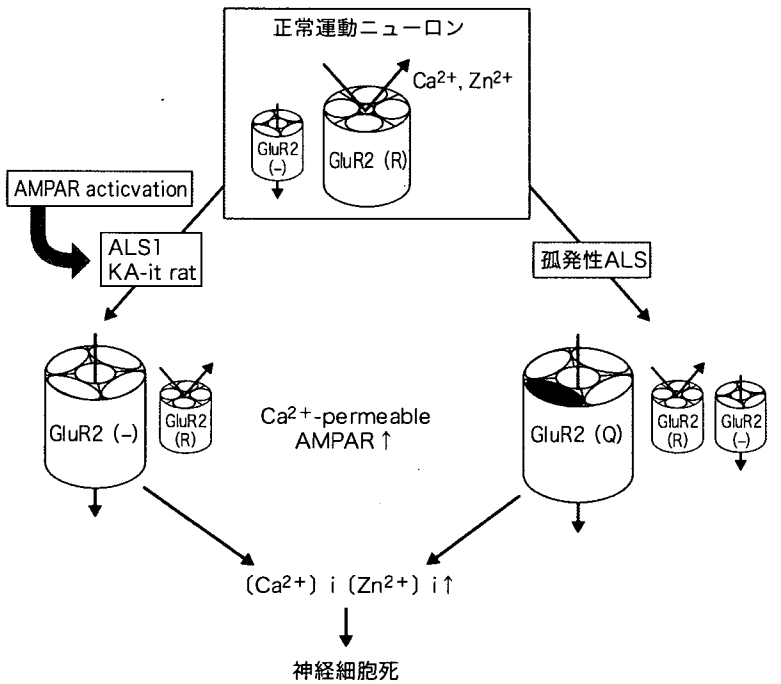

図3　AMPA受容体を介する運動ニューロンの神経細胞死の機序のまとめ（文献52を改変）
正常運動ニューロンではほとんどのAMPA受容体（AMPAR）は編集型GluR2（R）でありCa^{2+}を通さない．わずかながら運動ニューロンでGluR2を含まないCa^{2+}透過性の高いAMPARが存在することが知られている．本文中で述べたように孤発性ALS，ALS1のいずれにもAMPARを介した細胞死のメカニズムのエビデンスがあるが，両者のメカニズムは異なっている．孤発性ALSでは未編集型GluR2（Q）が増加することで透過性AMPARが増加し，一方でALS1ではGluR2の割合の減少により編集型GluR2を含まないAMPA受容体の割合が増加することで細胞内Ca^{2+}濃度が上昇し，神経細胞死が引き起こされる．ただし，前者が単独で神経細胞死が生じるのに対して，後者はSOD1の細胞毒性などの因子が加わる必要がある．

の運動ニューロンで選択的にADAR2活性が低下するのかを含め孤発性ALSの病態メカニズム解明が治療に結びつけられる成果が期待される.

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Power-Law Temporal Autocorrelation of Activity Reflects Severity of Parkinsonism

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Abstract: We aimed to obtain a reliable, objective scale representing disease severity for appropriate management of patients with Parkinson's disease (PD). Nineteen patients with PD at the Department of Neurology, Tokyo University Hospital, were classified into mild (n = 10) or severe groups (n = 9) depending on their Hoehn-Yahr scores, and wore accelerometers on their wrists for more than 6 consecutive days. During this time we monitored their subjective assessments of symptom severity and analyzed the power-law exponents (α) for local maxima and minima of fluctuations in the activity time series. Statistical comparisons were made between the severe and mild groups and of individual patients on "good condition" and "bad condition" days, as well as between days before and after antiparkinsonism medication. In all patients, the α for local maxima was always lower when parkinsonism was mild than when severe. Presence of tremor did not influence the α for local maxima. As the lower α value for local maxima of fluctuations in activity records reflects more frequent switching behavior from low to high physical activities or the severity of akinesia, actigraph monitoring of parkinsonism, and analysis of its power-law correlation may provide useful objective information for controlling parkinsonism in outpatient clinics and for evaluating new antiparkinsonism drugs. © 2007 Movement Disorder Society

Key words: Parkinson's disease; actigraph; akinesia; fractal analysis; power-law temporal autocorrelation.

A reliable objective scale representing disease severity is necessary for appropriate management of Parkinson's disease (PD) patients. Although the Unified Parkinson's Disease Rating Scale (UPDRS)[1] is a standard method for evaluating parkinsonism severity, UPDRS scores may not adequately reflect the disease severity. Wearable accelerometers (such as an actigram AMI, Ambulatory Monitors USA) enable long-term recording of patient's movement during activities of daily living, and hence might be the best choice for a device for quantitative assessment of the symptoms due to various diseases.[2-8] Recently, studies have been successful in developing reliable analytical methods that quantitatively represent the disease progression in patients with tremor.[9-11] Here, an analytical method sufficiently sensitive and reliable to represent the severity of non-tremor activity is presented.

Recently, fractal analysis was shown to be a robust tool to disclose hidden autocorrelation patterns in biological data, such as heartbeat and limb movement.[12-17] Power-law autocorrelation exponents for local maxima and minima of fluctuations of locomotor activity would be the most useful for our purpose, as they represent the level of persistency of movement patterns. In this study, we analyzed patients' physical activity records collected by an actigraph device using power-law exponents probing temporal autocorrelation of the activity counts. We found that the power-law exponent for local maxima most sensitively and reliably reflects disability without being influenced by the presence of tremor or the patterns of daily living.

PATIENTS AND METHODS

Nineteen patients with PD (13 male and 6 female; mean age ± SEM, 63.7 ± 9.8 years) at the Department

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TABLE 1. *The profile of subjects*

Patients	Age (year)	Sex	Hoehn and Yahr score		Duration of illness (year)	Tremor
			On	Off		
Pt. 1	54	M	2.0	3.0	5	+
Pt. 2	72	F	2.5	3.0	4	−
Pt. 3	41	F	2.0	2.5	7	−
Pt. 4	70	M	2.5	3.0	9	+
Pt. 5	57	M	2.0	2.5	10	−
Pt. 6	60	F	1.5	2.0	5	−
Pt. 7	65	M	1.5	2.0	5	−
Pt. 17	57	M	1.0	1.5	1.5	+
Pt. 18	42	M	1.5	2.0	8	−
Pt. 19	71	M	2.0	2.5	8	−
Mean ± SEM	*58.9 ± 3.52*		*1.85 ± 0.15*	*2.4 ± 0.16*	*6.25 ± 0.82*	
Pt. 8	60	F	3.5	4.5	6	−
Pt. 9	64	F	3.0	4.0	8	+
Pt. 10	60	M	3.0	4.0	10	−
Pt. 11	64	M	3.0	4.0	5	−
Pt. 12	70	M	4.0	4.5	10	+
Pt. 13	79	F	3.5	4.0	12	−
Pt. 14	60	M	3.0	3.5	20	−
Pt. 15	57	M	3.5	4.0	8	+
Pt. 16	73	M	4.0	4.5	7	−
Mean ± SEM	*65.22 ± 2.43*		*3.39 ± 0.14*	*4.11 ± 0.11*	*9.56 ± 1.49*	

Controls	Age (year)	Sex	Property	Profession
Con. 1	36	M	Healthy	Student
Con. 2	51	M	Healthy	Professor
Con. 3	28	F	Healthy	Technician
Con. 4	50	F	Healthy	Manager
Con. 5	32	M	Healthy	Student
Con. 6	30	F	Healthy	Student
Mean ± SEM	*37.83 ± 4.15*			

of Neurology of the Tokyo University Hospital participated in this study (Table 1). Depending on their Hoehn and Yahr scores, the patients were classified into mild ($\leq$3, mean ± SEM, 2.13 ± 0.13) or severe groups (>3, 3.75 ± 0.12). Three patients in the mild group and 3 in the severe group had resting tremor but only on their dominant sides. Patients had no overt dementia or depression. Six healthy control patients (3 female and 3 male; 37.8 ± 4.2 years) were recruited from volunteers at The University of Tokyo. The study was approved by The Ethics Committee of the Graduate School of Medicine, The University of Tokyo, and performed under the principles outlined in the Declaration of Helsinki.

A small, custom wristwatch-sized activity monitor, ECOLOG (ECOlogical neurobehavior LOGger), equipped with a computer (Ruputer Pro, Seiko Instruments, Chiba, Japan) was used in this study to register and quantify human physical activity. In its Zero-crossing mode (ZCM), the zero-crossing counts were integrated over 1-minute intervals and the data was stored in internal memory. The activity monitoring device is analogous in performance to the commercial Actigraph Mini-Motionlogger (Ambulatory Monitors, Ardsley, NY) which has frequently been used for studies of physical activity[2,18,19]; the correlation coefficient between activity counts measured simultaneously by both devices for 24 hours was 0.91 ± 0.02 and for awake-time alone 0.82 ± 0.03 (mean ± SD, n = 6) in healthy adults (Y. Yamamoto, unpublished observation). In this study, we recorded activity counts/min in the ZCM with a setting comparable to mode 13 of the Mini-Motionlogger (filter range of acceleration signals: 2–3 Hz, sensitive threshold: high, gain: low). After recording, data were transmitted to an external computer by software installed on the device.

Participants wore the ECOLOG on the wrist of their nondominant side, or on some occasions on both sides, for more than 6 consecutive days. Patients were asked to keep a diary in which they recorded their disability grade every 30 minutes. The diary scores were defined as follows: 0 (almost no activity), 1 (very difficult to initiate movement), 2 (difficulty in initiating movement), 3 (some difficulty in activities in daily living), and 4 (almost normal). They were also asked to write down the time they took pills and periods when they removed the ECOLOG. Because most of the patients could manage their daily living by themselves and reported feeling good when the proportion of diary scores at $\geq$3 exceeded

60% of the awake-time, we arbitrary classified the days into two categories based on this proportion; when more than 60% of the awake-time was scored as ≥3, the day was defined as a "good condition" (GC) day, and when less than 60% of the awake-time was ≥3, the day was defined as a "bad condition" (BC) day. Six of the PD patients, whose diagnoses included MRI findings, and who had not received any antiparkinsonism drugs wore the ECOLOG for more than 6 consecutive days both before the initiation of medication and after the stabilization of medication effects (Pt. 1, 2, 6, 7, 17, 18). The "after" study was conducted when the dose of the medication (2–3 mg of cabergoline or 0.45–0.75 mg of pergolide) was stable for more than 3 weeks in each patient.

We separated the data acquired during awake-time and sleep-time with Action-W, Version 2 (Ambulatory Monitors, Ardsley, NY) and the data during awake-time were used for analyses. To examine temporal autocorrelation of the physical activity time series (i.e., dynamic aspects of physical activity) we used an extended, random-walk analysis, the detrended fluctuation analysis (DFA),[13] with a recent modification[12] for various "real-world" signals including activity time series. The original DFA evaluates relationships between time scales and magnitudes of fluctuation (standard deviations) within each time scale; more correlated signals represent a greater growth of the fluctuation magnitude with increasing time scale or length of data window. It also eliminates nonstationarity in the input data (i.e., changes in the baseline and trends within the data windows at different scales) that could affect calculation of the magnitudes of fluctuation, thus making this approach suitable for the analysis of the long-term data collected in the present study. The power-law (scaling) exponent (α), obtained as the slope of a straight line fit in the double-logarithmic plot of time scales versus magnitudes of fluctuation, was used to characterize the level of such correlation. This index reflects the probability of a simultaneous increase or decrease in the variability at two distant points in time in the time series, applied to all distances up to long-range time scales, thereby probing the nature of "switching" patterns between high and low values in a statistical sense. Larger power-law exponents indicate positive temporal autocorrelation or persistency in the increase or decrease, and lower values correspond to negative autocorrelation or antipersistency.

Recently, Ohashi et al. reported that physical activity data have different power-law exponents in periods with higher and lower activity levels, corresponding to qualitatively different physiological states, (i.e., active and rest, respectively).[12] The actual procedures we used are

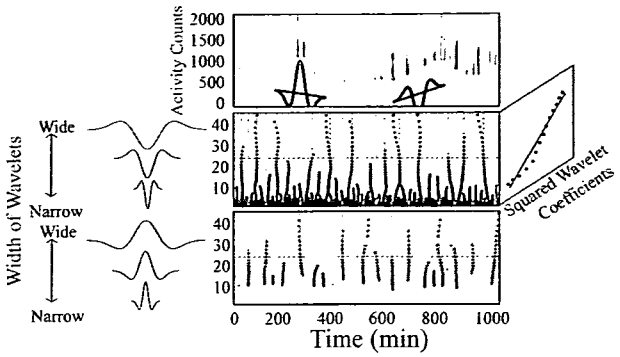

FIG. 1. Conceptual explanation of the method to obtain power-law exponents for local maxima and minima. (top) Various widths of hat-shaped wavelets are slid along the data to detect local minima (middle) and local maxima (bottom) of the wavelet coefficients. Note that the local minima and maxima appear at the transient decreases and increases of the activity, respectively. The power-law exponents are calculated from the slope of the log-log plot of squared wavelet coefficients versus the scale for local minima and maxima. In the actual analysis, we used an integrated, rather than raw, time series and $\psi(t)$, i.e., the derivative of the "hat-shaped" wavelet. This yields the same power-law exponents as those obtained by the DFA method for the same local maxima and minima as obtained in this figure (see Methods for details).

as follows: (see Ohashi et al. for details).[12] First, a daytime physical activity time series was integrated, as in DFA, and wavelets with different time scales (S) were slid along the time series and correlated with the data to obtain the wavelet coefficients ($W(S)$) at each point. We used the third derivative of the Gaussian function as the so-called "mother wavelet":

$$\psi(t) = t(3 - t^2)e^{-0.5t^2},$$

where t is time. This is equivalent to using the Gaussian second derivative (so-called "Mexican hat") wavelet to examine the raw signals (Fig. 1), though the integration approach automatically removes the local mean and the local linear trend, as in DFA. By changing the scale of the wavelet, this "hat-shaped" template dilates or contracts in time, probing transient increases or decreases in activity records in different time scales. The transient increases (low-high-low activity patterns) yield local maxima of the wavelet coefficients at their time points, while the decreases (high-low-high activity patterns) yield local minima of the wavelet coefficients (Fig. 1). Next, the squared wavelet coefficients at the local maxima or minima were averaged for all the available days. As the coefficient gives the magnitude of local fluctuations matching the shape of $\psi(t)$ with different time scales, the squared $W(S)$ was used, again as in DFA. Finally, the power-law exponent (α) was obtained separately for local maxima and minima as the slope of a

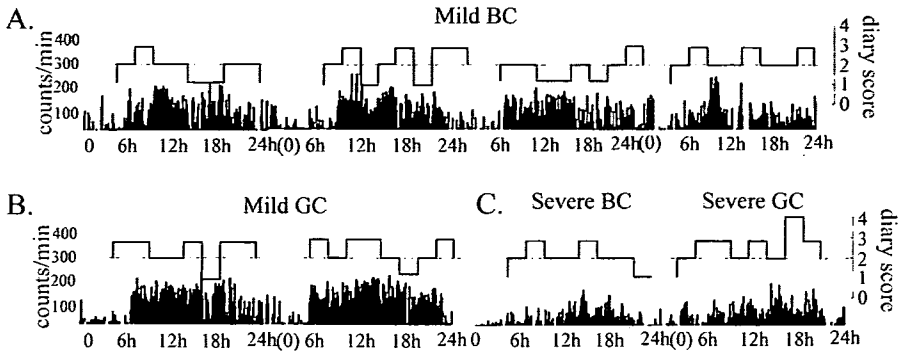

FIG. 2. Examples of daily activity profiles and the corresponding subjective, diary-based scoring on days in different conditions in patients with different disease severities. BC, bad condition day; GC, good condition day.

straight line fit in the double-logarithmic plot of S versus $W(S)^2$. In this study, the range of S corresponding to 8 to 35 minutes, where acceptable linear relationships between log S and log $W(S)^2$ were observed for all the records, was used. This range is also approximately the same as that used in Ohashi et al.[12] Note that this method yields the same α-values as does DFA,[20] but separately for periods with higher and lower activity levels. The power-law exponent α's of local maxima and minima were used to assess the quantitative disabilities during awake-time and the differences in disabilities between GC days and BC days, between before and after antiparkinsonism medication in individuals, between the severe and mild groups, and between groups with and without tremor. Records during 6 consecutive days were used in the analysis.

Wilcoxon signed rank tests were performed to compare α-values for local maxima or minima in the various group comparisons. P values < 0.05 were considered statistically significant.

RESULTS

The daily profile of physical activity exhibited robust activity-rest cycles but no apparent correspondence between daily activity profiles and diary scores (the mean activity counts vs. diary score: r = −0.063) (Fig. 2).

Average wavelet coefficients for local maxima and minima of the severe and mild groups provided straight lines in the range of 8 to 35 minutes (Fig. 3A), indicative of very robust α-values. When the mean α-values for local maxima and minima were compared, we found a significantly lower α-value for local maxima in the mild group than in the severe group (Fig. 3B). All the patients in both the severe and mild groups showed significantly lower α-values for local maxima on GC days than on BC days, whereas there was no significant difference in the mean α-values for local minima (Fig. 3C). When the effects of medication were examined, we found that all the patients showed lower α-values for local maxima, but not for

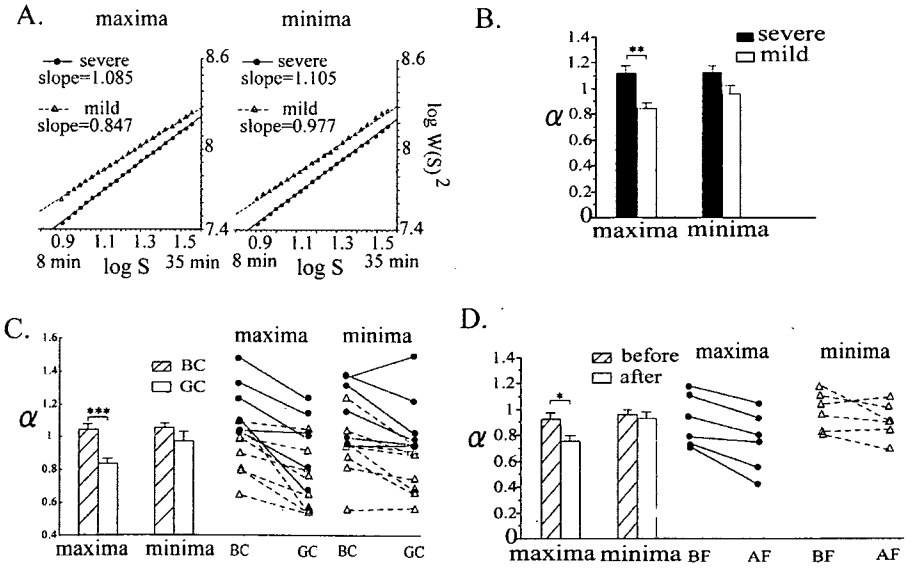

FIG. 3. Local maxima and minima of fluctuation of physical activity. (A) Average wavelet coefficients, as a function of the wavelet scale, for local maxima and minima. The slopes are power-law exponents, α. (B) Comparisons of the mean α for the severe and the mild groups, (C) for BC and GC days and for individual patients, and (D) for days before and after antiparkinsonism medication and for each patient. $^*P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$.

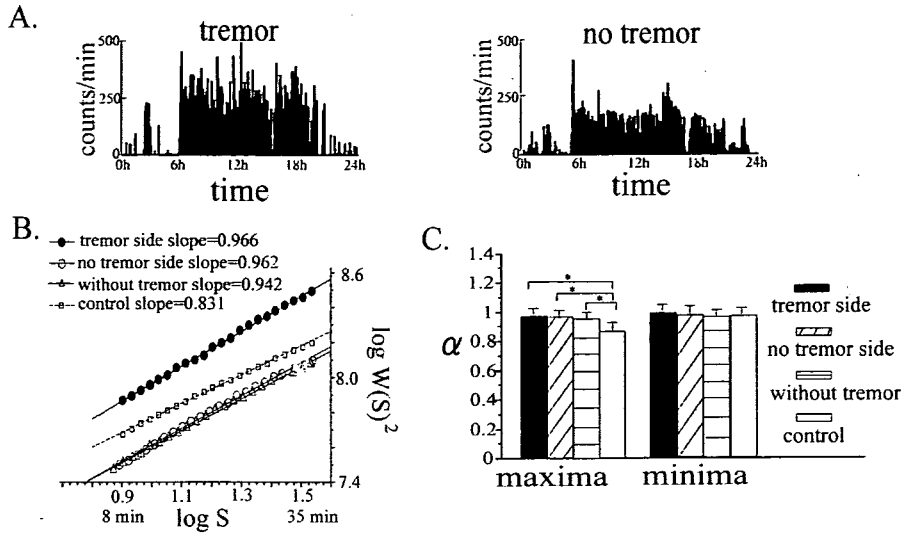

FIG. 4. Effects of tremor. (A) Daily profiles of physical activity for the arm affected with tremor and that without tremor of a patient with unilaterally predominant parkinsonism with continuous tremor on one side. (B) Average wavelet coefficients for local maxima among arms with tremor (tremor) and without tremor (no tremor). Arms of patients with tremor (n = 6), arms of patients without tremor (without tremor: n = 13), and control subjects (control: n = 6). (C) The power-law exponents for local maxima and minima. $*P < 0.05$.

local minima, on days after they received antiparkinsonism medication than on those before (Fig. 3D).

We compared the activity records from the arms with tremor and without tremor from 6 patients with tremor, and arms of patients not affected with tremor (n = 13). The activity counts in the arms with tremor were significantly higher than those in the arms without tremor (Fig. 4A). Power-law scaling of the records from arms with tremor showed a linear correlation between log S and log $W(S)^2$ in the range of 8 to 35 minutes (Fig. 4B) and α-values for local maxima but not for minima were significantly higher in patient arms than in control arms irrespective of tremor (Fig. 4C).

DISCUSSION

We demonstrated that analysis of records of a custom actigraph by the power-law temporal correlation is a powerful tool for the quantitative evaluation of physical activity in patients with parkinsonism. The diary-based subjective scoring of good or bad conditions was apparently not correlated with the objective daily profiles of physical activity recorded by the accelerometer, indicating that the activity counts themselves do not represent the patient's condition.

Larger power-law exponents (α) indicate positive temporal autocorrelation, or persistency, in the increase or decrease in the variability of activity at two distant points in time in the time series, and lower values correspond to negative autocorrelation or anti-persistency.[12] In other words, a lower α for local maxima or minima of activity records reflects more frequent switching behavior from low to high or high to low physical activity, respectively, and the switching behavior from lower to higher activity levels is considered to be related to akinesia in patients with parkinsonism. We found lower α-values for local maxima during GC days than during BC days, in the mild group than in the severe group, and before medication than after medication. Thus, these results demonstrate that the power-law analyses accurately describe the well known phenomenon that under these conditions patients switch their physical activity from lower to higher levels more easily, in other words they exhibit milder akinesia, when the parkinsonism is mild than when it is severe. It is worthy to note that lower α-values for local maxima were obtained for all the patients after medication than before, and when in GC than in BC, thereby providing a temporal profile of parkinsonism in each individual patient.

We adopted Mode 13 of the ECOLOG to record the motion range during daily living. This is compatible with the same mode of the AMI Mini-Motionlogger and is said to filter out the majority of movements with frequencies outside the 2 to 3 Hz range. Although some resting tremor in the 4 to 8 Hz range, found in typical parkinsonism or in a part of the "true " movement accelerations resulting from muscle force[21] might have been filtered out of our recordings, we found higher activity counts during awake-time on the arms with tremor, which erroneously indicated milder parkinsonism compared with the arms without tremor when judged from the level of activity counts. In contrast, the α-values for local maxima did not differ between the arms with tremor and those without tremor, but were significantly lower in both of the patient groups than in the control arms, indicating that although the presence of tremor

greatly influenced the actigraphic counts, the presence of tremor did not yield false positive results in the power-law exponent for maxima.

In conclusion, we found that the power-law exponent for local maxima sensitively and reliably reflects disability without being influenced by the presence of tremor or the pattern of daily living. Our results thus suggest that analysis of power-law temporal autocorrelation of physical activity time series using the bidirectional extension[12] is applicable to patients with parkinsonism for the evaluation of akinesia irrespective of the presence of involuntary movements including tremor and may provide useful objective data necessary for the control of drug dosage in the outpatient clinic and also for the evaluation of new drugs for parkinsonism.

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INTERNAL MEDICINE

□ SHORT COMMUNICATION □

Gabapentin for Painful Legs and Moving Toes Syndrome

Hitoshi Aizawa

Key words: gabapentin, painful legs, moving toes syndrome

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A 73-year-old woman presented with a 5-month history of continuous tingling pain in both feet. She had a past history of laminectomy at the level of the fourth lumbar vertebra due to the damage of lumbar intervertebral disc 7 years ago. Lumbar sympathetic blocks could calm the pain transiently. The patient had not an urge to move the legs or the toes. The symptoms did not change with rest or walking. On neurological examination, there were intermittent and irregular movements of the right toes, mainly of abduction and adduction. The patient could not suppress them voluntarily. There was no muscle atrophy, fasciculations nor myokymia. Muscle strength was normal. Tendon reflexes were normal except for ankle reflexes which were absent. Light touch, pinprick, cold sense and position sense were normal, however, vibration sense was slightly decreased at the distal lower extremities. Peroneal and posterior tibial motor nerve conductions were normal. Sural sensory nerve conduction was slightly decreased. MRI of the lumbar spine revealed no abnormality in the spinal cord or roots. Baclofen, clonazepam, carbamazepine and tricyclic antidepressants have been tried without success. Gabapentin (200 mg 3 times daily) was prescribed, with partial relief of the pain. Then, the pain could be controlled by 700 mg of gabapentin per day, however, movement of toes continued.

Discussion

Painful legs and moving toes syndrome may not be a homogenous entity (2, 3). At least two different physiopathologic mechanisms have been proposed: peripheral and central mechanisms (2, 3). Lesions in the posterior root ganglion, cauda equina, nerve roots, or a peripheral nerve can cause frequent impulses in afferent fibers which activate local circuits of interneuron and motoneurons resulting in local muscle movements. Pain and involuntary movement may also occur together in a central disorder (2, 3), although the precise mechanism is still under investigation.

A variety of medications, such as baclofen, benzodiazepines, tricyclic antidepressant, anticonvulsant, beta-blockers, and corticosteroids, have been tried in painful legs and moving toes syndrome previously, usually with disappointing results. Gabapentin was initially produced as an adjunctive antiepileptic drug, its indications now include diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, migrain prophylaxis, bipolar disorder and anxiety disorders.

Gabapentin is structurally related to the neurotransmitter GABA, although it has no direct GABAergic action on GABA receptors. Gabapentin seems to enhance inhibitory input of GABA-mediated pathways. It has an inhibitory effect on voltage-dependent calcium ion channels at the postsynaptic dorsal horns and may interrupt the series of events leading to the neuropathic pain (4). Gabapentin has been clearly demonstrated to be effective for the treatment of neuropathic pain in diabetic neuropathy and postherpetic neuralgia (4). Therefore, gabapentin should be considered an important drug in the management of other neuropathic pain syndromes such as painful legs and moving toes syndrome, although there is only one previously reported case successfully treated with gabapentin (5).

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INTERNAL MEDICINE

□ CASE REPORT □

An Adult Case of Relapsing Human Herpesvirus-6 Encephalitis

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Abstract

Human herpesvirus-6 (HHV-6) is the main etiologic agent of exanthema subitum in young children. Central nervous system (CNS) infections in children due to HHV-6 have been described on many occasions. HHV-6 is also a common cause of infections in immunocompromised individuals. However, little is known concerning the impact of HHV-6 on the CNS in immunocompetent adults. We report the first case of relapsing HHV-6 encephalitis in a healthy 73-year-old female.

Key words: human herpesvirus-6 (HHV-6), relapse, encephalitis, immunocompetent

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Introduction

Human herpes virus-6 (HHV-6) was first isolated in 1986 from patients with lymphoproliferative disorders or HIV infection, and it has been identified as the causal agent of exanthem subitum in young children (1, 2). Central nervous system (CNS) disorders such as febrile seizures, meningoencephalitis, and encephalopathy may complicate the course of HHV-6 primary infection in children (3, 4). HHV-6 is also a common cause of infections in immunocompromised individuals (4). However, CNS infection induced by HHV-6 is very rare in immunocompetent adults, and the pathogenesis of these cases remains unclear (5-14).

Here, we report the first case of relapsing HHV-6 encephalitis in an immunocompetent 73-year-old female.

Case Report

A 70-year-old healthy female was admitted to our hospital with disorientation after tonic-clonic seizures in June 2002. She had been well until one month earlier, when she began to feel general fatigue. She had no anamnesis and had never gone abroad. Neurological examinations revealed disturbance of consciousness, right Chaddock sign, and frontal sign. Blood cell counts were normal and blood serum and chemistry showed mild liver dysfunction and elevation of C reactive protein (CRP). Analysis of cerebrospinal fluid (CSF) showed a protein increase (85 mg/dl) with a normal leukocyte count (3 cells/mm^3). Magnetic resonance imaging (MRI) performed in early July revealed high intensity lesions at the bilateral basal ganglia on a T2-weighted image and a fluid attenuated inversion recovery image (Fig. 1A). Oral antiepileptic drugs (phenytoin: 30 mg and phenobarbital: 100 mg per day respectively) were started after admission. But drug-induced skin eruptions appeared on her hip the next day, and the rashes extended to her trunk, limbs and face with high fever on the following day. Therefore the treatment of phenytoin and phenobarbital was discontinued, and oral prednisolone (30 mg per day) was administered from the same day. Improvement of the skin rashes and fever were seen from mid-July, and the eruption was disappeared by the end of July. Her consciousness improved gradually, and she left the hospital two months after admission with mild cognitive impairment. HHV-6 IgG antibody titer of the serum which was collected three days after admission, was elevated to 80 -fold (reference value is less than 10 -fold), and decreased to 10 -fold early in July, while the serum IgM antibody was not elevated. The abnormalities on MR images disappeared by April 2003.

In January 2005, she complained of general fatigue. She became disorientated with a slight fever of 37.8℃ in early February and was readmitted to our hospital. Neurological examinations revealed disturbance of consciousness and bi-

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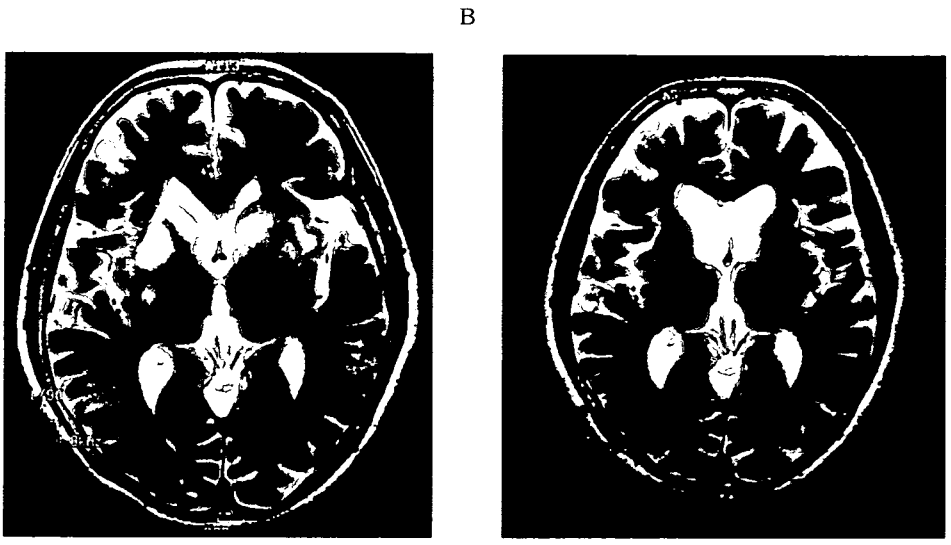

Figure 1. MRI findings on T2-weighted image of this patient. A: There were wide high intensity lesions at bilateral basal ganglia on the 19th day of the first hospitalization. B: There was no intracranial abnormal lesion including basal ganglia on the 20th day of the second hospitalization.

lateral patellar hyperreflexia. Signs of meningeal irritation were not observed. Her blood cell count was normal, and blood serum and chemical studies showed neither liver nor renal dysfunction. CRP was not elevated. CSF analysis performed on the admission day revealed increase in leukocytes (32 monocytes/mm^3) and protein (102 mg/dl) with a normal glucose level. Bacterial, fungal, and mycobacterial cultures of the CSF were all negative. Human herpesvirus simplex (HSV) PCR was negative, and cytology showed no malignant cells. Electroencephalography showed a diffuse slowing, but no seizure discharge. Brain computed tomography performed in early February revealed no abnormal lesion. Because viral encephalitis was suspected from the clinical findings and CSF analysis, aciclovir (ACV) was started immediately, but her consciousness disturbance did not improve. Skin rashes appeared three days after admission, and corticosteroids were administered. She could speak after a few days, and skin eruptions disappeared. After three weeks, she could walk with support. Brain MRI findings at the end of February revealed no abnormal lesion apart from mild atrophy of bilateral frontal lobe (Fig. 1B). HHV-6 IgG antibody titer of the serum which had collected in mid-February was significantly elevated (maximum value: 320-fold), and decreased to 20-fold with improvement of consciousness by mid-March, while serum IgM antibody was not elevated. Neither anti-HHV-6 IgG nor IgM antibodies were elevated in the CSF. The CSF was not examined for HHV-6 DNA because the volume collected was insufficient. Blood HHV-6 DNA was not detected. Furthermore, neither IgG nor IgM antibodies to other herpesvirus (including HSV-1, varicella-zoster virus, cytomegarovirus, and Epstein-Barr virus) and Japanese encephalitis virus were abnormally elevated. From these results, we assumed that this relapsing encephalitis might be caused by HHV-6. Finally, she was discharged without any sequelae fifty-one days after hospitalization.

Discussion

HHV-6 is the main etiologic agent of exanthema subitum in young children, and has been implicated as a possible cause of encephalitis in pediatric patients (1-4). Epidemiologic studies have shown that most people are infected with HHV-6 at an early age. The virus remains latent state in lymphocytes, salivary glands, and brain tissue after primary infection, and has been reactivated in immunocompromised patients (15, 16). Encephalitis caused by HHV-6 has occasionally been documented in immunocompromised individuals, e.g., HIV-positive patients; recipients of bone marrow transplants, liver transplants, and renal transplants; and persons with lymphoproliferative disorders (1, 17, 18). However, there are few reports on the involvement of HHV-6 in the CNS in immunocompetent adults suffering from meningitis and/or encephalitis (5-14). Furthermore, there is no report of relapsing encephalitis due to HHV-6 in an immunocompetent adult. The present non-immunocompromised patient experienced a recurrence of HHV-6 encephalitis, which is very rare.

After primary infection, HHV-6 is characterized by lifelong latency in peripheral blood monocytes, salivary glands, and brain tissue (15, 16). HHV-6 seems to be a resident virus of human brain and is able to cause a restricted or minimally productive infection of brain cells, including microglial cells, astrocytes, and oligodendrocytes (16). There have been several reports that suggest the direct invasion of HHV-6 into the CNS. The frequency of detecting the HHV-6 genome by PCR in the brain tissue of immunocompetent adults was reportedly between 15% and 85% (19, 20). One group demonstrated HHV-6 DNA in 57% of brain tissues obtained from AIDS patients (21). Reactivation of infection occurs occasionally during pharmacological immunosuppres-

sion or acquired immunodeficiency. Thus, HHV-6 may be considered an important opportunistic pathogen. In contrast, immunocompetent adults very rarely have HHV-6-induced CNS infection (5-14). In the present case, the serum HHV-6 IgG antibody was elevated in the early stage and decreased afterward, while the serum IgM antibody against HHV-6 was not elevated. The considerable increase of IgG antibodies without a positive IgM antibody titer indicates reactivation of the virus (14), but its cause is unknown. One possibility is that the pathogenic mechanism involved in HHV-6 meningitis/encephalitis in immunocompetent adults may be related to the ability of HHV-6 to evade host immune responses through various mechanisms; induction of CD4 lymphocyte depletion via apoptosis, down-regulation of CD3 expression in T cell clones infected in vitro, a decrease of peripheral blood lymphocyte proliferation by HHV-6 via transcriptional down-regulation of IL-2, and decreased generation of reactive oxygen intermediates from monocytes that were infected with HHV-6 in vitro (22). Another undeniable possibility is that the patient had an immunocompromising disease that had not been diagnosed. In the present case, ACV was administered because the etiology was uncertain at first, but ganciclovir (GCV) and foscarnet were demonstrated to be more effective than ACV for some immunosuppressed patients with HHV-6 induced encephalitis (17, 18).

According to the past literature about immunocompetent patients with HHV-6 induced encephalitis, the majority (80%) of the patients presented with an altered level of consciousness; 60% had seizures, and 55% had focal neurological signs (9). Meningeal irritation, weakness of limbs, hyperreflexia, ataxia and visual disturbance were reported as the neurological findings. Analysis of CSF revealed mild-moderate increase of leukocytes (monocytes-dominant) and proteins in almost cases. In about half cases there were CT or/and MRI abnormal findings at CNS: including basal ganglia, thalamus, cerebral white matter, brain stem, and spinal cord, but there were no lesion at CNS in the other cases (5-14).

The first symptom of our patient was disturbance of consciousness and tonic-clonic seizures, but the only recurring symptom was disturbance of consciousness. The MRI findings in the first hospitalization revealed bilateral basal ganglia lesions, but there was no obvious lesion on MRI in the second hospitalization. The reason is unknown, but we assume that the degree of second HHV-6 reactivation was more subtle, and therefore the clinical features due to HHV-6 were different in the same individual. It is reported that basal ganglia lesion on MRI is often observed in encephalitis caused by some viruses such as Japanese encephalitis virus, Nipah virus, West Nile virus (23-25). Because serum antibody levels to Japanese encephalitis virus were not elevated in our case and the patient had never gone abroad, it was thought that these viruses were not the cause of encephalitis in this patient.

Drug-induced hypersensitivity syndrome (DIHS) is characterized by a severe, potentially fatal, multiorgan hypersensitivity reaction. DIHS usually occurs 3 weeks to 3 months after starting a limited number of drugs, including carbamazepine, phenytoin, phenobarbital, dapsone, mexiletine, salazosulfapyridine, alloprinol, and minocycline. The diagnosis of DIHS is confirmed by the presence of five of the following six criteria: 1) macuropapular rash developing > 3 weeks after starting therapy with the above drugs, 2) lymphadenopathy, 3) fever, 4) leukocytosis, 5) hepatitis, 6) HHV-6 reactivation (26). HHV-6 encephalitis associated with DIHS was reported previously (27). In the present case, a skin rash with high fever appeared soon after the dosage of phenytoin and phenobarbital in the first hospitalization. Our case can not be said to satisfy this DIHS criteria, as it lacked the following criteria: lymphadenopathy, leukocytosis, and hepatitis. But the skin rash appeared in both the first and the second hospitalization, which may also be related to encephalitis by HHV-6.

It is particularly unusual for a person not in an immunocompromised state to suffer from relapsing encephalitis due to HHV-6. We should consider the possibility of HHV-6 in the differential diagnosis of encephalitis in immunocompetent adult patients when the viral etiology of meningoencephalitis is unknown.

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