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神経症候群（第2版）

—その他の神経疾患を含めて—

IV

VIII　先天異常/先天奇形

破壊性獲得性二次性障害

大脳萎縮症

小坂　仁

破壊性獲得性二次性障害

大脳萎縮症

Cerebral atrophy

小坂　仁

Key words：アポトーシス，ネクローシス，白質，灰白質

1. 概念・定義

大脳が形成された後の何らかの破壊，萎縮による細胞死による大脳萎縮．

2. 疫　　学

我が国における大規模な調査はなく不明である．

3. 病　　因[1-3]

1）出生前の異常

a. 母体環境によるもの

a）母体疾患によるもの

妊娠中毒症，糖尿病，甲状腺疾患，高血圧，膠原病などは，胎盤機能不全などを通じて大脳萎縮を生じさせる可能性がある．

b）薬剤による影響

向精神薬，抗痙攣薬，アルコール，麻薬，麻酔薬など

b. 胎内感染

トキソプラズマ，風疹ウイルス，サイトメガロウイルス，単純ヘルペスウイルス感染など

c. 染色体異常，代謝性疾患などの遺伝子異常による疾患

2）周産期異常

仮死，血管障害，分娩外傷など

3）出生後の異常

(1) 代謝異常などの遺伝子異常による疾患

(2) 感染，脳症，脳血管障害，外傷など後天性疾患

4. 病　　態[1]

中枢神経系の構成細胞であるニューロン，オリゴデンドロサイト，アストロサイトなどに，不可逆的な細胞傷害が起き，細胞死が起こることによる萎縮性変化が基本病態である．未熟な細胞に生じる障害は成人期と異なる反応を示す．細胞死の分子機構を図1に示す．

細胞死には，従来顕微鏡学的に細胞膜が消失し，細胞内小器官が浮腫し，空胞化しタンパク分解酵素やDNA分解酵素が活性化しクロマチンが無秩序に分解されDNAがスメア様に分解を受けるネクローシスおよび，ATPを用い，分解酵素のカスパーゼによって担われ，DNAがラダー状に分解を受ける細胞死であるアポトーシスが知られている．新生児低酸素性虚血性障害の研究などより，アポトーシスとネクローシスは厳密に区別されるものではなく，一連の反応であることがわかっている．

5. 診断と鑑別診断(表1)[1-5]

遺伝性疾患には非常に多くの鑑別診断が存在するため，MRIにより画像的に病変の主体が灰白質(ニューロン)か白質(オリゴデンドロサイトなど)で分類し，灰白質も，皮質，深部灰白質に分け，白質も皮質下白質，深部白質かで分け分類する．また病変が，髄鞘化不全によるものはこれらから鑑別し，臨床・検査所見から原因診断に至る．

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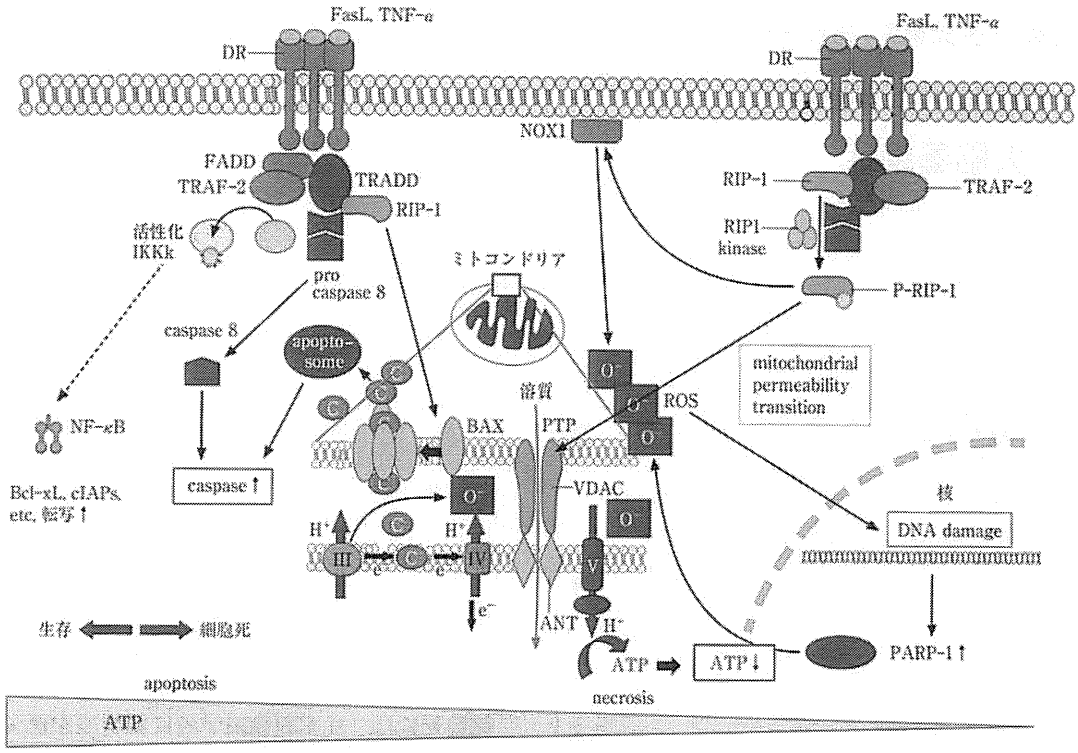

図1　様々な細胞死と生存(文献[1]より引用)

Fasリガンド(FasL), tumor necrosis factor(TNF)-αといった, 細胞死誘導作用のあるサイトカインがTNF受容体superfamily(death receptors: DR)に結合すると, 受容体は, 3量体になる. この3量体はFAS-associated protein with death domain(FADD), TNFR-associated factor(TRAF)-2, receptor interacting protein(RIP)-1, TNFR-associated death domain(TRADD)などと複合体を形成する.

生存状態：(図の左端)十分にATPのある状況では, IκB kinase(IKKk)のリン酸化が起き, nuclear factor-κB(NF-κB)の核内誘導を起こしB-cell lymphoma-extra-large(Bcl-xL), inhibitors of apoptosis(cIAPs)などの, アポトーシス阻害に働くタンパクの転写誘導を促す.

アポトーシス：(図の左側)ATPの低下状態では, RIP-1により, pro caspase 8が分解され, 下流のカスパーゼを活性化し(外来性経路)あるいはBaxがミトコンドリア外膜に4量体のチャンネルを形成し, cytochrome C(C)が細胞質に流入, procaspase-9などとapoptosomeを形成しさらにカスパーゼシグナルを増強させる.

ネクローシス：(図の右半分)さらにATPが低下した状態においては, RIP1キナーゼの作用下, NADPH oxidase(NOX1)がreactive oxygen species(ROS)を生成し, さらにはvoltage depedent anion channel(VDAC), adenine nucleotide transporter(ANT)などからなるmitochondrial transition pore(PTP)を開口させmitochondria, permeability transitionにより細胞内溶質がミトコンドリア内に流入し, 浮腫を起こす(programmed necrosis). 最もATP枯渇の状況ではDNAダメージが通常は, DNA修復に働くpoly ADP-ribose polymerase-1(PARP-1)の強い活性化により, ミトコンドリアのプロトン勾配を破壊し, ATPのさらなる枯渇を招き, 活性化酸素の上昇を招きそれがDNA障害をさらに強める.

6. 治療と予後

多くは, 対症療法となる. 白質病変は筋緊張亢進に至る場合が多く筋弛緩剤が用いられる. 深部灰白質病変では, 不随意運動を伴うことが多いため不随意運動緩和薬, 皮質灰白質病変ではてんかんを伴うことが多いため, 抗てんかん薬が用いられる.

また原因治療が可能な疾患(**表1**で#のついた疾患)では, 速やかに治療を開始するとともに, 原因確定以前でも診断的治療を行うことも考慮する.

予後は, 疾患により異なる.

表1 大脳萎縮症(遺伝性)の分類

白質病変が主体の疾患

1. 深部白質から病変が始まる疾患

a. 異染性白質ジストロフィー症
(アリルスルファターゼAやスフィンゴリピド活性化タンパクB異常による，スルファチドの蓄積)

b. クラッベ病 #(一部で骨髄移植)
(ガラクトシルセラミダーゼ活性低下によりガラクトシルセラミドが蓄積)

c. 副腎白質ジストロフィー #(早期の骨髄移植)
(ペルオキシゾームのトランスポーター異常による極長鎖脂肪酸分解阻害)

d. vanishing white matter型白質脳症
(EIF2B1-5異常により，ストレスに際してタンパク合成を停止する小胞体ストレスの不全)

e. 巨大軸索ニューロパチー
(中間型フィラメントの構造異常)

f. *フェニルケトン尿症 #(食事療法)
(フェニルアラニン水酸化酵素活性低下による)

g. *メープルシロップ尿症 #(食事療法)
(分枝鎖アミノ酸α-ケト酸脱水素酵素複合体の異常)

h. *ホモシステイン尿症 #(葉酸，ビタミンB_6)
(シスタチオニンβ合成酵素異常)

i. 5,10メチレンテトラヒドロ葉酸還元酵素欠損 #(ベタイン，コバラミン，葉酸)
(尿中ホモシスチンと血中のメチオニンが低値)

j. コバラミン代謝異常 #(コバラミン)
(iに加えメチルマロン酸尿症を伴う)

k. ビオチニダーゼ欠損症 #(ビオチン)
(ビオチンの生成不全のビオチニダーゼ欠損症とホロカルボキシラーゼ欠損症からなる)

l. メチオニンSアデノシルトランスフェラーゼ欠損症
(高メチオニン血症をきたす)

m. Lowe症候群
(phosphatidylinositol-4,5-biphosphate-5 phosphatase欠損による，ゴルジ輸送系異常)

n. メロシン欠損性先天性筋ジストロフィー症
(lamina-α-2異常)

o. ムコリピドーシスIV型
(mucolipin-1異常により，カルシウム輸送およびライソゾーム輸送系異常をきたす)

p. 脳梁低形成を伴う劣性痙性対麻痺 spatacsin(SPG11)およびspatizin(SPG15)

q. シェーグレン・ラーソン症候群
(fatty aldehyde dehydrogenase欠損，ALDH3A2遺伝子他複数の遺伝子が関与)

2. 皮質下白質に脱髄の主座をもつ疾患

a. 皮質下嚢胞を伴う巨脳白質脳症
(MLC1あるいはHEPACAM異常，いずれも機能不明)

b. Aicardi-Goutières syndrome(アイカルディ・グティエール症候群)
(DNA修復に関わる遺伝子異常)

c. コケイン症候群
(DNA修復障害)

d. *ガラクトース血症 #(乳糖制限)
(ガラクトース代謝に関わる酵素欠損による)

3. 髄鞘化不全による疾患

a. ペリツェウス・メルツバッヘル病
(proteolipid protein 1の異常)

b. ペリツェウス・メルツバッヘル様病1
(gap junction proteinの異常)

c. 基底核および小脳萎縮を伴う髄鞘形成不全症
(チュブリンTUBB4Aの異常による)

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（表1つづき）

d. 18q−症候群
（ミエリン塩基性タンパクの欠失が原因）
e. アラン・ハーンドン・ダドリー症候群
（monocarboxylic acid transporter 8欠損による甲状腺ホルモン膜輸送障害）
f. サラ病
（SLC17A5異常によるライソゾームへのシアル酸蓄積）
g. 小脳萎縮と脳梁低形成を伴うびまん性大脳白質形成不全症
（RNA polymerase IIIをコードするPOLR3AおよびPOLR3B異常）
h. 先天性白内障を伴う髄鞘形成不全症
（FAM126A(DRCTNNB1A)異常によるオリゴデンドロサイトの分化への関与が示唆）
i. 失調，歯牙低形成を伴う髄鞘形成不全症
（RNA polymerase IIIのサブユニットをコードするPOLRIIIA遺伝子の異常）
j. 脱髄型末梢神経炎，中枢性髄鞘形成不全症，Waardenburg症候群，Hirschsprung病
（SOX10異常による神経堤由来細胞の発生異常）

4. 種々の白質病変を取りうる疾患

a. 非ケトーシス型グリシン血症
（グリシン開裂系異常による高グリシン血症）
b. ジヒドロピリミジン脱水素酵素欠損症
（ウラシルとチミンの代謝酵素．尿中チミンとウラシルが上昇するピリミジン代謝異常症）
c. 3−ヒドロキシ−3−メチルグルタリル補酵素Aリアーゼ欠損症
（ロイシンと脂肪酸代謝に関わる．有機酸代謝異常）

灰白質が主体の疾患

1. 深部灰白質が主

a. パントテン酸キナーゼ関連神経病(ハラーホルデン・スパッツ病)
（パントテン酸キナーゼ2異常により鉄の貯留が起こる）
b. 若年性ハンチントン舞踏病
（ハンチンチンのCAGリピート延長）
c. イソ吉草酸血症　#(L−カルニチン，ロイシン制限)
（イソバレリルCoA脱水素酵素異常によるイソバレリン酸貯留）
d. コハク酸セミアルデヒド脱水素酵素欠損症
（GABAと4−hydroxybutyric acidが蓄積）
e. クレアチン欠損症　#(一部でクレアチン，オルニチン投与)
（クレアチン合成酵素もしくはクレアチントランスポーター異常）

2. 皮質が主たる病変の疾患

a. 神経セロイドリポフスチン症
（*CLN1*～*CLN8*など複数遺伝子関与，一部はアポトーシスに関わる）
b. ニーマン・ピック病　#(C型でミグルスタット投与)
c. レット症候群
（転写因子MECP2異常）
d. アルパース症候群
（ミトコンドリアDNAポリメラーゼ異常による）
e. 乳児神経軸索ジストロフィー
（ホスホリパーゼA2欠損により，神経軸索にスフェロイド形成が起こる）
f. アスパルチルグルコサミン尿症
（アスパルチルグルコサミナーゼ異常によるオリゴ糖症）

皮質灰白質と白質が障害される疾患

1. 深部灰白質は保たれるもの

a. アルパース病

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(表1つづき)

b. メンケス病
c. ムコ多糖症
d. 脂質蓄積症
e. ペルオキシソーム病

深部灰白質と白質が傷害される疾患

1. 視床病変が強い疾患

a. クラッベ病
b. GM1ガングリオシドーシス
(β-ガラクトシダーゼ)
c. GM2ガングリオシドーシス
(β-ヘキソサミニダーゼA, B)
d. ウィルソン病 #(銅キレート剤)
(ATP7B異常による血中, 胆汁中への銅の排泄異常)

2. 淡蒼球病変が強い疾患

a. カナバン病
(アスパルトアシラーゼ欠損によりアスパラギンと酢酸が減少し, ミエリンタンパク合成低下)
b. カーンズ・セイヤー症候群
(ミトコンドリアDNAの粗大欠失や重複による)
c. メチルマロン酸血症 #(ビタミン B_{12} 投与)
(メチルマロニルCoAムターゼ異常あるいは補酵素のビタミン B_{12} の利用異常)
d. *メープルシロップ尿症
e. L-2-ヒドロキシグルタル酸尿症
(L-2-ヒドロキシグルタル酸分解酵素異常)
f. フコシドーシス
(α-フコシダーゼの異常によるオリゴ糖症)
g. 歯状核赤核淡蒼球ルイ体萎縮症
(小児に最も多い脊髄小脳変性症)
h. 尿素サイクル異常症

3. 線条体(尾状核, 被殻)病変が強い疾患

a. リー症候群
b. MELAS
(ミトコンドリア脳筋症・乳酸アシドーシス・脳卒中様発作症候群)
c. ウィルソン病
d. アレキサンダー病
(glial fibrillary acidic proteinがアストロサイトに異常蓄積)
e. エチルマロン酸血症
(ミトコンドリアのマトリックスで硫黄の分解に関わる分子の異常)
f. プロピオン酸血症 #(食事療法)
(プロピオニルCoAカルボキシラーゼ)
g. グルタル酸尿症I型 #(L-カルニチン投与, ロイシン, トリプトファン制限)
(グルタリルCoA脱水素酵素欠損症:前側頭葉形成不全をみる)
h. 3-ヒドロキシ-3-メチルグルタリル補酵素Aリアーゼ欠損症
i. モリブデン補酵素欠損症
(モリブデン補酵素の合成障害のため, 種々の酸化酵素特に亜硫酸酸化酵素活性が低下)
j. 3-メチルグルタコン酸尿症
(多くの代謝異常で起こる, 一部はロイシンの代謝異常)
k. βケトチオラーゼ欠損症
(脂肪酸からのケトン体産生に関わる酵素の欠損)

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（表1つづき）

l. マロン酸血症
（ロイシン，イソロイシン代謝最終に関わるマロニルCoAデカルボキシラーゼ欠損）
m. ビオチニダーゼ欠損症　#（ビオチン投与）
（ホロカルボキシダーゼ合成酵素欠損も含む）
n. ビオチン依存性大脳基底核症　#（ビオチン投与）
（ビオチンがチアミントランスポーターの発現を制御）
o. コケイン症候群

*新生児マススクリーニング対象疾患．

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てんかんの原因

ミトコンドリア異常症

代表的な原因疾患

三牧正和

定義，病態

- ミトコンドリア異常症は，ミトコンドリアの一次的機能低下に起因する疾患の総称である．慢性進行性外眼筋麻痺（CPEO）[*1]，MERRF[*2]，MELAS[*3]の3大病型，Leigh脳症などの多様な病型を包含する疾患概念である[*4]．
- ミトコンドリアは生体のエネルギー産生をつかさどる細胞内小器官であり，赤血球以外の全身の細胞に存在する．その機能低下は多組織にわたる障害を生じるため，本症は多彩な臨床症状を呈する．
- なかでも神経系はエネルギーに大きく依存しているため，神経症状[*5]を呈する患者は多い．脳卒中様発作，てんかん，ミオクローヌスなど，けいれん[*6]を呈する発作性病態は本症の臨床上重要である．
- ミトコンドリア異常症でけいれんが高率に合併することは，ミトコンドリア機能異常が神経系にけいれん源性をもたらすことを意味し，エネルギー産生障害がもたらす細胞機能低下，活性酸素種の漏出による細胞の酸化的損傷などが関与していると考えられている．

症状，検査

- 原因不明の脳卒中様発作やけいれん，ミオクローヌス，とくに多彩な臓器障害を認めた場合には，本症を念頭におき検索を進める[*7]．

MERRF

- 小脳症状と筋症状を主症状とし骨格筋病理所見にragged-red fiber[*8]を伴う疾患で，10歳前後で進行性ミオクローヌスてんかん[*9]の臨床像をとる[1]．
- ミオクローヌスはほぼ必発であり，約70％の患者では初発症状として発症し，症例の約70％で全般けいれん発作を認める[2]．
- 脳波では，発作時の棘徐波複合などの異常波に加え，基礎波の徐波化を認めるが，疾患に特異的な所見はない．光過敏性や，体性感覚誘発電位（SEP）での巨大SEPを認めることがあり，大脳皮質の興奮性を示唆する．

MELAS[*10]

- 脳卒中様症状[*11]と高乳酸血症を特徴とし，初発症状は脳卒中様症状とけいれんが多い．脳卒中様発作がけいれんを伴う場合以外に，症候性てんかんを合併する場合がある．また，てんかんとして治療されていた患者が脳卒中様症状を起こし確定診断される症例も散見する．
- 脳卒中様発作の病変が後頭葉に強いことを反映し，視覚症状を伴う部分発作重積を経験することもある．
- 脳波上は局所的，片側または全般の徐波とてんかん波を認めることがある．脳卒中様発作急性期では，多棘波を伴う局所的な高振幅δ波が高率に認められるとの報告もあるが，いずれも疾患特異性はない．

Leigh脳症

- 幼児期以前から発症する精神運動発達遅滞および退行，神経画像上大脳基底核中心の左右対称性病変，血中・髄液中の乳酸・ピルビン酸の高値を特徴とする[*12]．
- 食事摂取障害・体重増加不良，発達遅滞・退行，筋緊張低下，眼球運動異常，視神経萎縮・視力障害が多いが，けいれんを呈し慢性化したてんかんの病態に至る例もある[*13]．

治療

急性発作時の治療

- てんかん症状出現期にミトコンドリア機能異常に起因する代謝の破綻をきたしている場合があり，乳酸・ピルビン酸値，血液ガス分析は必須である．
- 乳酸アシドーシスには輸液[*14]やアルカリ剤の静脈内投与による補正を行う．
- けいれん発作を呈している場合や，脳波上のてんかん重積状態にある場合は，抗てんかん薬投与を迅速に行い鎮痙させる．
- 意識障害時には，けいれんを伴わない症例においても，脳波による複雑部分発作重積の鑑別が必要である．
- 筋緊張・筋力低下のある症例や，Leigh脳症など脳幹病変をきたしている例では，抗てんかん薬投与による呼吸抑制にはとくに注意が必要である．

寛解期の維持療法

- 乳酸の蓄積防止とエネルギー産生障害の改善を目的として，種々の薬物（ユビデカレノン〈ノイキノン®〉，コハク酸，ジクロロ酢酸など）が有効であったという報告があるが，効果は明らかにされていない．
- 本症のてんかんに対する特異的な治療法はなく，発作型に合わせた抗てんかん薬による治療を選択する[*15]．
- ミオクローヌスや全般てんかんに有効であるバルプロ酸は，カルニチン合成を阻害してミトコンドリア機能低下を惹起するため，使用しない．

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*1 **CPEO**
ミトコンドリアDNA（mtDNA）の単一欠失や多重欠失が原因であることが多い．多重欠失を示す例では，ANT1，POLG，TWINKLEなどの核DNAに変異が報告されている．POLG変異については，ミトコンドリアDNAの量的低下をもたらすことがあり，難治てんかんを呈するAlpers症候群の原因となる．

CPEO：chronic progressive external ophthalmoplegia

*2 **MERRF**
mtDNAのm.8344A＞G変異を90％の患者に認める．

MERRF：myoclonus epilepsy associated with ragged-red fibers

*3 **MELAS**
mtDNAのm.3243A＞G変異，m.3271T＞C変異などのtRNA領域の遺伝子異常が原因であることが多いが，一部にm.13513G＞A変異などのタンパクコード領域の変異も認める．

MELAS：mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes

*4 代表的な病型をとらない非特異的なミトコンドリア異常症も多くみられる．ミトコンドリア異常症の診断においては，従来の病理組織の形態的変化のみならず，ミトコンドリアの主要な機能を担う呼吸鎖複合体の量的・質的評価や酵素活性測定による異常の検出が重要である．

*5 **ミトコンドリア異常症の神経症状**
精神遅滞や退行，眼球運動などの脳神経症状，小脳失調，不随意運動，頭痛，中枢性呼吸障害など症状はさまざまである．

*6 **けいれんの合併**
ミトコンドリアにはカルシウムイオンが高濃度で貯蔵されているため，ミトコンドリア障害がカルシウムホメオスタシスの破綻をもたらし，神経細胞の膜興奮性が亢進してけいれんを誘発することも考えられる．

*7 頭部MRIなどの神経画像異常や，血中・髄液中の乳酸・ピルビン酸の高値が手がかりになることが多い．

*8 **ragged-red fiber**
赤色ぼろ線維．異常に増加したミトコンドリアがGomori trichrome変法で染色された像で，ミトコンドリア病における骨格筋ミトコンドリアの形態異常を示す病理変化の一つ．

*9 **進行性ミオクローヌスてんかん**
ミオクローヌスは不随意運動の一つであり，素早く反復する律動的な筋収縮をさす．ミオクローヌスとてんかんが併存し，精神や運動退行などを呈する進行性の病態や疾患群を，進行性ミオクローヌスてんかんという．

SEP：somatosensory evoked potential

*10 てんかん発作型はMERRFよりも多彩で，全身性強直間代けいれん，単純部分発作，複雑部分発作が報告されている[3]．発作重積としては，全身けいれん重積以外に，部分発作重積の報告もある[4]．また，意識障害が高頻度に認められると報告されているが，そのなかに複雑部分発作が含まれている可能性がある．

*11 脳卒中様症状は頭痛や嘔吐，片麻痺，皮質盲などからなり，脳画像における急性の局所異常所見を認めることがある．

*12 m.8993T＞Gなどのミトコンドリア DNA変異をもつ症例もあるが，多くは核遺伝子変異による．呼吸鎖の複合体Ⅰの構成タンパク（NDUFV1，NDUFA1，NDUFS4など），複合体Ⅳの構成タンパクなどの欠損で，てんかんやけいれんの報告がある．また，呼吸鎖の集合に関わる核性因子（FOXRED1など）の異常でも，てんかんやけいれんを伴うLeigh脳症をきたすことが明らかになってきている．

*13 ピルビン酸脱水素酵素欠損などによる場合は，West症候群の合併が多い．

*14 筆者らの施設では，乳酸を含有せず，かつアシドーシスの補正に有利な重炭酸リンゲル液（ビカーボン注®）を初期輸液として使用している．糖を含有しないため，ブドウ糖を混注する．カリウム濃度が低く維持輸液としては不向きなため，細胞外液補充後はフィジオ35®などを使用する．ビタミンの補充も十分に行う．

*15 クロナゼパムなどのベンゾジアゼピン系薬剤や，カルバマゼピンなどが一定の効果を示すが，病期の進行に伴い増悪し，コントロールが困難になることも多い．

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Brain imaging for oxidative stress and mitochondrial dysfunction in neurodegenerative diseases

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Oxidative stress, one of the most probable molecular mechanisms for neuronal impairment, is reported to occur in the affected brain regions of various neurodegenerative diseases. Recently, many studies showed evidence of a link between oxidative stress or mitochondrial damage and neuronal degeneration. Basic *in vitro* experiments and postmortem studies demonstrated that biomarkers for oxidative damage can be observed in the pathogenic regions of the brain and the affected neurons. Model animal studies also showed oxidative damage associated with neuronal degeneration. The molecular imaging method with positron emission tomography (PET) is expected to delineate oxidatively stressed microenvironments to elucidate pathophysiological changes of the *in vivo* brain; however, only a few studies have successfully demonstrated enhanced stress in patients. Radioisotope copper labeled diacetyl-bis(N^4-methylthiosemicarbazone) (Cu-ATSM) may be the most promising candidate for this oxidative stress imaging. The tracer is usually known as a hypoxic tissue imaging PET probe, but the accumulation mechanism is based on the electron rich environment induced by mitochondrial impairment and/or microsomal over-reduction, and thus it is considered to represent the oxidative stress state correlated with the degree of disease severity. In this review, Cu-ATSM PET is introduced in detail from the basics to practical methods in clinical studies, as well as recent clinical studies on cerebrovascular diseases and neurodegenerative diseases. Several other PET probes are also introduced from the point of view of neuronal oxidative stress imaging. These molecular imaging methods should be promising tools to reveal oxidative injuries in various brain diseases.

KEY WORDS: Positron-emission tomography - Neuroimaging - Oxidative stress.

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Oxidative stress is considered to be one of the principal molecular mechanisms of neuronal impaired and degenerative conditions in various neurodegenerative diseases such as parkinsonian syndromes, motor neuron diseases including amyotrophic lateral sclerosis (ALS), Alzheimer's disease and other dementias.[1-3] There are a number of basic studies indicating that oxidative stress plays a major role in neuro-degeneration and astrocyte dysfunction in model animals and *in vitro* experiments. Postmortem studies also demonstrated the brain oxidative damage in these diseases pathologically and biochemically.[2-4] However, only a few reports demonstrated visual evidence of oxidative stress occurred in the *in vivo* human brains of those patients.

Oxidative stress is induced by various causes and mechanisms such as mitochondrial dysfunction, inflammatory changes and environmental toxins. Classically, it is defined as an imbalance of the reduction-oxidation (redox) state, where generation of reactive oxygen species (ROS) exceeds the capacity of cellular antioxidant defense systems. When the ROS exceed this capacity, the oxidative stress induces neuronal degeneration, as well as apoptosis or cell death in the brain.[5, 6] The central nervous system is vulnerable to excessive oxidation, because

neurons and glial cells require immense energy and oxygen consumption, but the brain has fewer antioxidant defense systems compared with other organs.[7] Excessive production of ROS provokes oxidative stress, which leads to damage to nucleic acids, proteins, and lipids, and these processes result in cellular dysfunction.

A lot of findings in previous papers suggested significant effects of oxidative stress on degenerative changes in the brain and spinal cord in neuronal disorders; however, the degree of oxidative injury in the neurodegeneration process of *in vivo* patients' brains has been difficult to evaluate. One of the major causes of enhanced ROS production and oxidative stress is an over-reduction state due to impairment of the mitochondrial respiratory chain, which induces leakage of excessive electrons. Indeed hypoxic changes in the brain due to vascular impairment are one of the representative conditions of oxidative injury and mitochondrial dysfunction. Several ligands have been developed for *in vivo* molecular imaging to determine hypoxic tissues in the brain and myocardium, as well as tumor hypoxia. However, whether these tracers for hypoxic tissue imaging are equally suitable to delineate oxidative stress conditions in the brain regions of pathologic changes is still controversial and remains unclear.

Molecular brain imaging for oxidative stress and mitochondrial dysfunction

A lot of ligands have been developed for visualization of hypoxic conditions in the brain, myocardium and other organs, as well as hypoxic tissues in tumors. Some of the representative probes for positron emission tomography (PET) are nitroimidazole analogs, such as [^{18}F]- fluoromisonidazole (^{18}F-FMISO), [^{18}F]-fluoroerythronitroimidazole (^{18}F-FETNIM), 1-(5-[^{18}F] fluoro-5-deoxy-α-D-arabinofuranosyl)-2-nitroimidazol (^{18}F-FAZA), [^{18}F]-1-(2-fluoro-1- [hydroxylmethyl]ethoxy)methyl-2-nitroimidazole (^{18}F-FRP170), and so on.[8] ^{18}F-FMISO, the most widely used hypoxia imaging tracer, was proposed as a PET tracer to determine tumor hypoxia *in vivo* in 1984.[8] Many studies have been published on a relationship between tumor hypoxia and ^{18}F-FMISO PET including tracer accumulation mechanism and kinetic analysis; however, studies on its application to brain hypoxia and ischemic change were relatively limited.[9-12] ^{18}F-FMISO has high enough lipophilicity for penetration of the cell membrane easily, and receives a reversible single-electron reduction by nitroreductase enzymes in the mitochondrial electron transport chain.[13] Its retention is dependent on the absence of molecular oxygen which induce re-oxidization and washout of the tracer, and thus, the accumulation usually reflects a decrease in tissue oxygen tension. The mechanism of tracer retention may indicate that ^{18}F-FMISO and related compounds are ideal probes for hypoxic tissue imaging; however, because of the slow tracer kinetics and prolonged washout, target-to-background contrast is hampered.[14] The second generation of nitroimidazoles for PET, such as ^{18}F-FETNIM and ^{18}F-FAZA, were developed to achieve better contrast of the hypoxic region.[8] The poor contrast may be a drawback of the slight changes in brain imaging of neuronal degenerative changes and oxidative stress.

Another promising hypoxic tissue imaging probe is radioactive copper labeled diacetyl-bis(N^4- methylthiosemicarbazone) (Cu-ATSM), which was developed to delineate an over-reduction state in cells or tissues caused by impairment of mitochondrial respiratory chanes.[15-17] This PET tracer can be used for imaging of mitochondrial dysfunction, which induces oxidative stress, because of its mechanism of accumulation, in addition to tumor hypoxic tissue imaging.[18, 19] A lot of studies have been published using Cu-ATSM to visualize tumor hypoxia, and ischemic myocardial and cerebrovascular diseases.[20-30] One of the advantages of this tracer is the wide variety of radioactive copper isotopes for labeling. Several radioactive copper isotopes with different half-lives, such as ^{60}Cu, ^{61}Cu, ^{62}Cu, ^{64}Cu and ^{67}Cu, can be used for labeling the tracer depending on the purposes of studies and settings at each institute, hospital, or clinical or basic research facility.[31] Tracer accumulation occurs within 5 min after the intravenous injection, and tracer distribution is not affected by different types of the copper isotopes used for labeling except for the background activity determined by the waiting time for the tracer washout.[23, 32] A shorter half-life radiotracer enables repeated PET scans for a single patient within a day, and a longer half-life tracer provides possibility of long time dynamic and follow-up scans with multiple frames. We used ^{62}Cu, a generator-derived radionuclide, for Cu-ATSM studies. The daughter radionuclide of ^{62}Cu has a half-life of 10 min and the parent radionuclide of ^{62}Zn has a longer half-life of 9 hours. Thus, the tracer can be

eluted from a generator system every hour during a whole day for clinical use.[15, 16]

Cu-ATSM is a stable Cu(II) complex developed as an hypoxia-selective imaging compound with a high membrane permeability due to its high lipophilicity. The retention mechanism of radioisotopes in cells is based on reduction of copper from a divalent form [Cu(II)] to a monovalent form [Cu(I)] under excessively over-reduced microenvironments such as hypoxia and oxidative stress. The reduced Cu(I) dissociates from the ATSM complex and is eventually trapped irreversibly in the cells.[15, 16, 22-24] Previous studies reported that in the hypoxic myocardium, a high concentration of nicotinamide adenine dinucleotide (NADH) resulted in Cu-ATSM accumulation through reduction of radioactive copper by a mitochondrial electron transport chain enzyme (NADH dehydrogenase) in an NADH-dependent manner.[15, 21] The retention mechanism in the hypoxic brain tissue is assumed to be similar to that in myocardial hypoxia. On the other hand, in tumor cells, Cu-ATSM reduction is reported to be mediated by NADH cytochrome b5 reductase and/or nicotinamide adenine dinucleotide phosphate (NADPH) cytochrome P450 reductase located in the microsome/cytosol fraction, rather than in the mitochondria, in an NADH/NADPH-dependent manner.[18]

Recently, Holland et al. showed that the hypoxia selectivity of Cu-ATSM arises due to a delicate equilibrium using advanced spectroelectrochemical techniques with computational analysis.[33, 34] In their experiment, the rate of reduction, which is presumed to be enzyme-mediated, re-oxidation and protonation in cells or tissues are fast relative to the rate of pH-mediated ligand dissociation. These results indicate that the accumulation of Cu-ATSM may not directly delineate reduction of oxygen tension, or rather, the presence of a high NADH/NADPH concentration with dynamic changes in intracellular pH induced by over-reduction of tissues under oxidative stress. These regions still maintain a viable, but damaged, mitochondrial or microsomal enzyme system. Thus, the accumulation of Cu-ATSM in the brain mainly depends on mitochondrial function rather than oxygen tension, which is the most different point from the accumulation mechanism of nitroimidazole compounds. Indeed, basic *in vitro* experiments showed that an increase in ^{64}Cu-ATSM retention was observed in cell lines under an over-reduction condition due to mitochondrial respiratory chain failure.[17,19] These studies demonstrated that an over-reduction state induced high levels of Cu-ATSM retention, indicating the possibility of oxidative stress imaging. Moreover, our previous reports showed an elevation of ^{62}Cu-ATSM accumulation in *in vivo* brains of ischemic changes in cerebrovascular diseases and neurodegenerative disorders, which was assumed to be induced by oxidative stress.[27, 28, 30] Based on all of these findings, Cu-ATSM seems to be a promising PET ligand for *in vivo* delineation of oxidative stress conditions in the brain in neuronal disorders.

Development of direct ROS imaging in tissues has also recently been started for PET. Chu et al. developed a new PET tracer for ROS imaging, which was selectively oxidized by superoxide, but not by other ROS, which may be able to achieve specific oxidative stress imaging caused only by superoxide.[35] Further studies are expected to develop direct ROS imaging *in vivo*.

PET procedure for ^{62}Cu-ATSM

There are several options for imaging of oxidative stress in human brains *in vivo*; one of the most promising PET tracers should be ^{62}Cu labeled Cu-ATSM because of its user friendly features. ^{62}Cu solution is available every hour eluted from a ^{62}Zn/^{62}Cu generator system based on the transient equilibrium of the longer half-life of the parent and the shorter half-life of the daughter nuclide. ^{62}Cu-ATSM can be obtained by a simple mixture of ^{62}Cu glycine solution and ATSM solution (0.5 mM in dimethyl sulfoxide) in a sterilized vial.[15, 28-30] The radiochemical purity of ^{62}Cu-ATSM is usually confirmed by the HPLC method using authentic unlabeled Cu-ATSM.

^{62}Cu-ATSM PET scans are performed for the whole brain scanning with 20 to 30 min dynamic frames or a list-mode protocol.[27, 28, 30] The PET scan is performed with an intravenous slow injection of 444—740 MBq ^{62}Cu-ATSM, and the dynamic scan procedure is started with a standard protocol of frame durations; a short frame length in the early phase and longer frames in the later phase. In our institute, the PET data are reconstructed with a filtered back-projection algorithm using a Hanning filter with a resolution of 5.0 mm full width at half maximum (FWHM) in the transaxial direction.

The ^{62}Cu-ATSM images are usually converted into semiquantitative images in a unit of standardized uptake value (SUV). The SUV is the ratio of the decay corrected radioactivity per unit volume

of tissue to the administered radioactivity per unit of body weight [(tissue MBq / g)/(injection MBq / BW kg)]. Early- and delayed-phase images are calculated by averaging the dynamic PET data for the first 3 min and the last 10 or 20 min of frames, respectively.[27, 28, 30] The first 3 min average image represents blood flow distribution in the brain and the later phase image reflects final retention of radioactive copper due to the reduction process. The latter image can be used for evaluation of oxidative stress closely linked with an over-reductive state.[27, 30]

In data analysis, the images can be applied to Statistical Parametric Mapping (SPM; Wellcome Department of Cognitive Neurology, London, UK) analysis and/or the region of interest (ROI) methods. The early phase image is usually used for anatomical normalization because the tracer accumulation is greater in this phase compared with the late phase image.[28] Using the parameters obtained from the anatomical transformation, the late phase image is also normalized into the standard brain space. This transformation process facilitates comparisons of relative uptake across subjects. In the study of cerebrovascular disease by Isozaki et al., delayed-to-early ratio images of Cu-ATSM calculated from a division process of the delayed phase (i.e. retention image) and the early phase (i.e. perfusion-like image) images provided new parametric information similar to oxygen extraction fraction (OEF) images in ^{15}O-gas PET studies.[30]

Different radioisotopes of copper can be applied to the brain imaging depending on the purpose of the study and facilities of the institute, but obtaining initial phase PET data is recommended for additional information on brain structure and perfusion.

Imaging of cerebrovascular diseases

Ischemic cerebrovascular disease caused by stenotic or obstructive changes in the major cerebral arteries may induce hemodynamic impairment, and chronic impairment with cerebral hypoperfusion may induce chronic oxidative stress, which finally leads to hypoxic damage in the brain.[36, 37] The classical model of the dynamic physiological change in cerebral hemodynamics has already been established; vasodilatory compensation as the first step, followed by the second step of cerebrovascular disease called "misery perfusion", a reduction of blood supply against the normal oxygen consumption for energy metabolism. Substantial hypoxic changes may occur after these steps and neurons under impaired hemodynamics will be damaged.[37] Oxidative stress should be observed in the later phase of the second to the early third stage. OEF increases in the misery perfusion phase, but the cerebral metabolic rate of oxygen ($CMRO_2$) remains in normal range until the advanced stage or later phase of misery perfusion. When oxidative stress occurs, the failure of the respiratory chain caused by mitochondrial damage provides excessive electrons, and Cu-ATSM accumulation increases in such conditions. Significantly high accumulation could be observed only in cases of irreversible mitochondrial damage;[27] however, only a slight increase in accumulation would be observed in conditions of viable and reversible damage to mitochondria. Since precise quantification of Cu-ATSM brain images has not been established, relative accumulation images or the delayed-to-early phase ratio images (see above) are usually used for evaluation.[30] The new parametric image of Cu-ATSM delayed-to-early ratio is expected to provide similar information to OEF, which is very useful in evaluation of hemodynamic impairment. The asymmetry index (AI) of the delayed-to-early ratio image is well correlated with that of OEF.[30]

An impressive case of mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) was reported recently, in which Cu-ATSM PET showed different accumulation patterns in various phases of acute, subacute and chronic stages of strokes (Figure 1).[27] MELAS is mainly caused by an A-to-G transition at nucleotide position 3243 (A3243G) in mitochondrial DNA (mtDNA).[38] The strokes in these patients are caused by a spastic stenotic change in the major cerebral arteries, and a focal and spontaneous ischemic change is induced. In the later acute to subacute phases of the stroke, patients showed normal cerebral blood flow and increased Cu-ATSM accumulation, indicating that oxidative stress and/or mitochondrial dysfunction occurred in the regions of stroke despite no arterial stenoocclusive change at the time of the PET scan.[27, 39] In such conditions, the lactate level in the region is increased in MR spectroscopy studies, indicating hypoxic stress or neuronal damage has taken place in the focal region of the stroke.[40]

Several studies using ^{18}F-FMISO for *in vivo* imaging of hypoxic changes in the brain have been

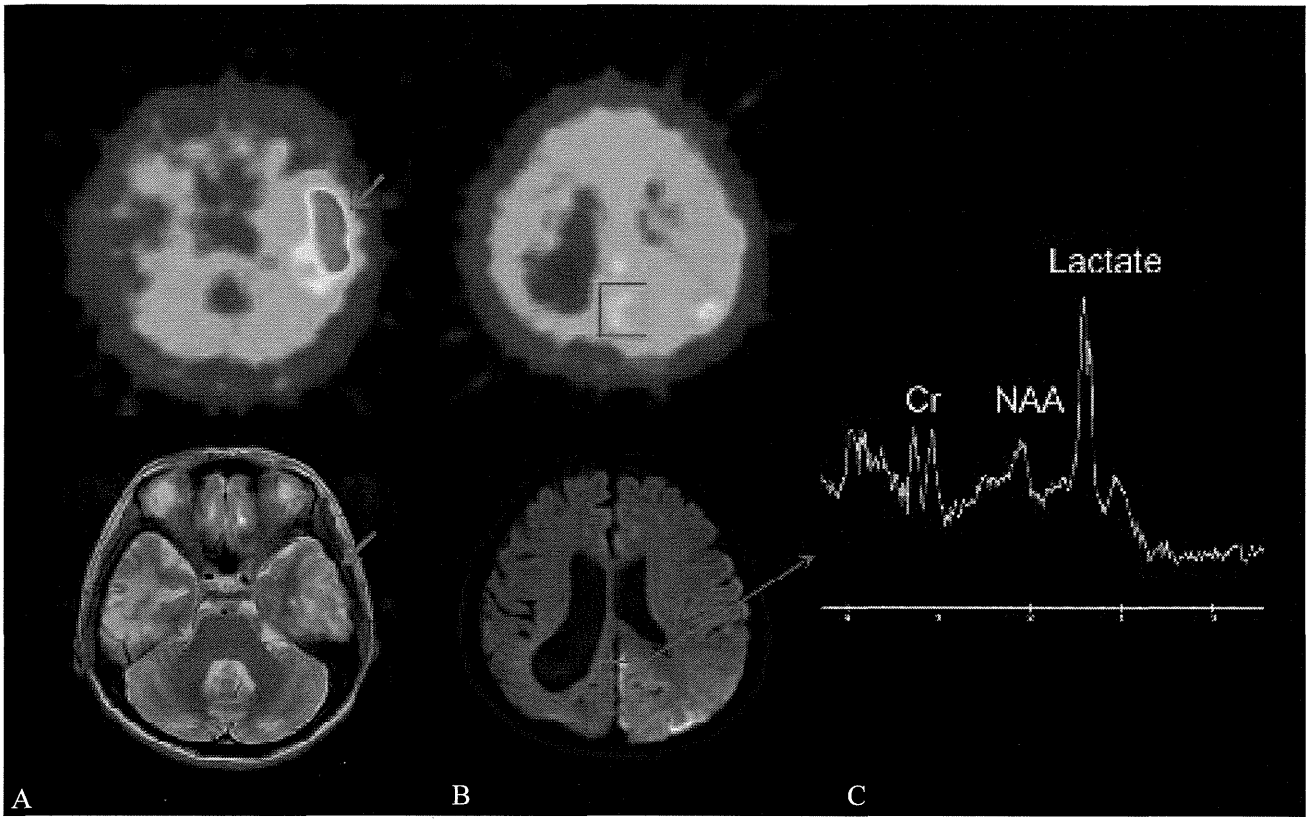

Figure 1.—Delayed phase ^{62}Cu-ATSM PET (top) and corresponding MRI (bottom) for a patient with MELAS. (A) Subacute phase of stroke in the left temporal lobe (arrow) shows high accumulation of ^{62}Cu-ATSM. Note the old infarction in the right temporal lobe shows a decrease in tracer uptake; B) acute phase of stroke shows moderate accumulation of ^{62}Cu-ATSM (red square) and an increase in regional lactate concentration on MR spectroscopy (C).

reported, but the findings are controversial.[9-11, 41, 42] Takasawa *et al.* reported a preliminary study with a middle cerebral artery (MCA) occlusion model of rats using ^{18}F-FMISO.[9] In their study, ^{18}F-FMISO was only accumulated under the regional condition of reduced oxygen tension by obstruction of the artery. Reperfusion by removing the MCA occluder washed out the accumulated tracer due to re-oxygenation of the affected brain regions. The results suggested that accumulation of ^{18}F-FMISO was determined simply by the oxygen tension regardless of the state of oxidative stress in the affected tissue or cells. On the other hand, Sarrafzadeh et al. reported high accumulation of ^{18}F-FMISO in affected region by aneurysmal subarachnoidal hemorrhage but preserved blood flow measured by perfusion CT.[10] They also reported that no anaerobic metabolism was observed in the high uptake region of ^{18}F-FMISO analyzed by microdialysis.

Parkinson's disease

Parkinson's disease is the second most common age-related neurodegenerative disorder with a prevalence of 1-2% in the 65 years and older population.[43, 44] Depletion of striatal dopaminergic function due to loss of neurons in the substantia nigra, and appearance of Lewy bodies in the remaining neurons are diagnostic neuropathologic findings.[45, 46] Although the primary etiology and pathogenesis of Parkinson's disease remain unknown, a number of studies have indicated that genetic and environmental factors, especially oxidative stress, contribute to degenerative changes in the dopaminergic neurons in this disease.[47] Postmortem studies reported that the brains of Parkinson's disease patients showed increases in the levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG), protein carbonyls and/or 4-hydroxynonenal (HNE), and lipid peroxidation products

in the nigrostriatal dopaminergic system.[4, 48-51] Additionally, in a study with basic *in vitro* experiments, Hashimoto et al. showed that ferric ion induced α-synuclein aggregation, one of the major causes of Parkinson's disease, in the presence of hydrogen peroxide.[52] Their result suggests that increased ROS levels may contribute indirectly to the pathogenesis of Parkinson's disease by causing α-synuclein aggregation, which can exacerbate further progression of the disease, in addition to direct dopaminergic depletion induced by neuronal damage.

In cases of autosomal recessive Parkinson's disease, causal mutations such as parkin, PTEN-induced putative kinase 1 (PINK1) and Parkinson protein 7 (PARK7, DJ-1), are associated with mitochondrial protein.[53-55] PINK1 is a mitochondrial kinase associated with protection against various stresses which may induce mitochondrial dysfunction.[56] Furthermore, reports on impairment of the mitochondrial respiratory chain in the nigrostriatal system suggest that mitochondrial damage also contributes profoundly to facilitation of dopaminergic cell dysfunction owing to enhancement of oxidative stress.[57, 58] Thus, mitochondrial dysfunction linked with oxidative stress in the nigrostriatal dopaminergic system is one of the most probable causes in Parkinson's disease, and visualization of mitochondrial impairment under an oxidatively stressed microenvironment should provide reliable pathophysiological evidence of the disease.

Based on these assumptions, we applied oxidative stress imaging to delineate striatal neuronal damage and dopaminergic depletion in Parkinson's disease.[28] ^{62}Cu-ATSM PET was performed in

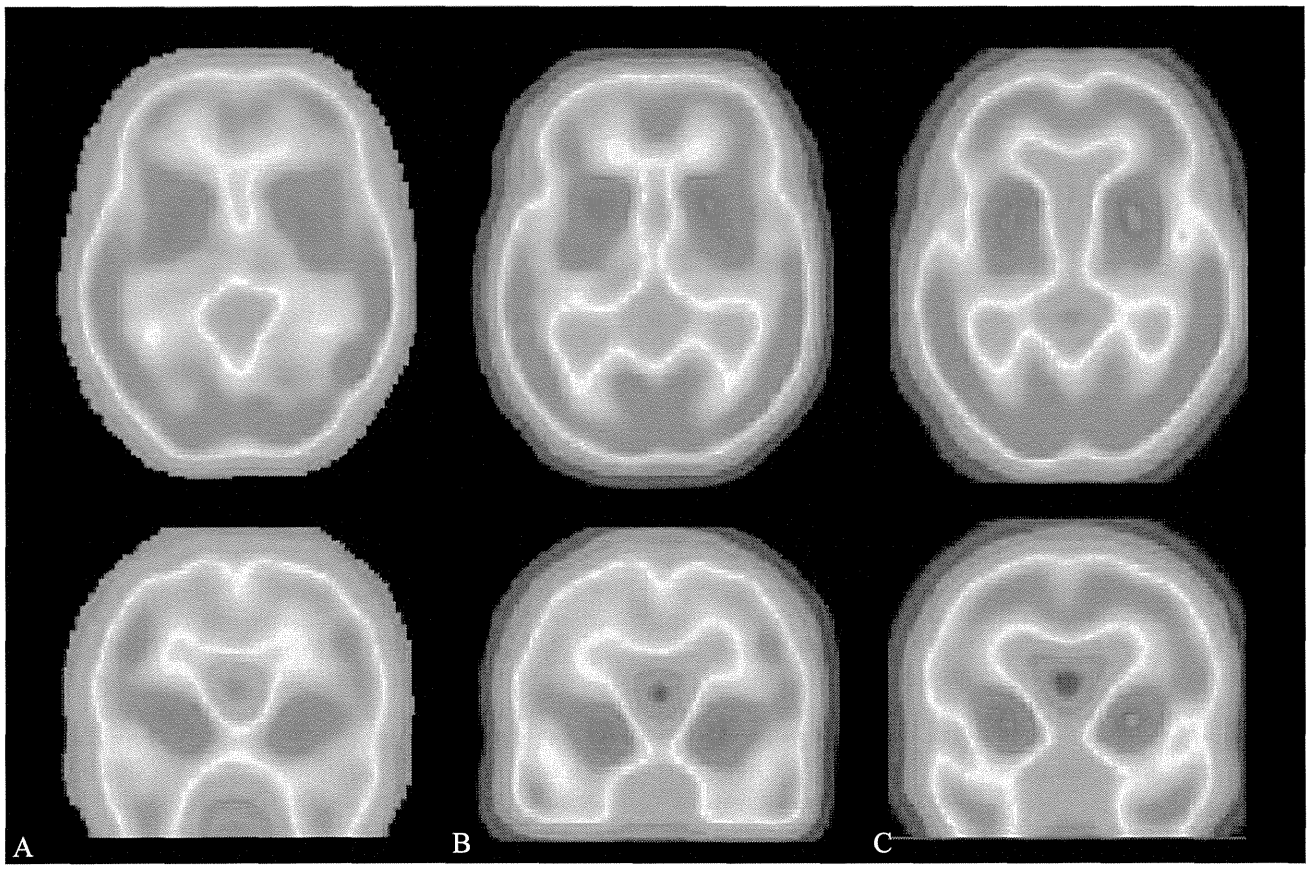

Figure 2.—Average images of younger healthy control (A, N.=6, mean age =35±9 y), older healthy control (B, N.=10, mean age =61±8 y) and patients with Parkinson's disease (C, N.=15, mean age =70±8 y) in a ^{62}Cu-ATSM PET study. The striatum shows increased ^{62}Cu-ATSM accumulation in older people compared with younger people, and significant elevation in patients. Images suggest increases in oxidative stress associated with age and degenerative changes. Top: transaxial view; bottom: coronal view.

groups of patients with sporadic Parkinson's disease and healthy controls, and the results showed a significant increase in striatal tracer accumulation in the patient group (Figure 2). The result indicated that mitochondrial impairment in the nigrostriatal dopaminergic neuron system was probably induced by oxidative stress and the *in vivo* oxidative damage was visualized successfully using Cu-ATSM PET.

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease in adults, and a fatal neurological disease characterized by the progressive degeneration of both upper and lower motor neurons.[3, 59] Various pathophysiological mechanisms have been proposed as contributors to sporadic ALS, such as glutamate excitotoxicity, protein aggregation, disruption of axonal transport, RNA processing defects, endoplasmic reticulum stress, and inflammation, as well as mitochondrial dysfunction.[60] Although the definitive cause of the disease remains unknown in sporadic ALS without a genetic component, various postmortem and biochemical investigations showed that oxidative stress and mitochondrial mitochondrial damage were very likely to be the most probable and principal molecular mechanism of motor neuron degeneration in ALS.[3, 61, 62]

Several postmortem studies reported that the brains of ALS patients showed increased levels of 8-OHdG, protein carbonyls or 4-HNE-histidine in the motor cortex and/or spinal cord, which are similar findings to the nigrostriatal dopaminergic neurons in Parkinson's disease.[63-66] Concentrations of 8-OHdG or 4-HNE in the blood, urine, and CSF of ALS patients were also reported to be increased compared with healthy controls in recent studies.[67-69] In addition, the studies showed a positive correlation between serum 4-HNE or urine 8-OHdG levels and severity of disease or clinical stage evaluated by the ALSFRS-R score in ALS.[67, 69] However, these biochemical or pathological studies merely provide collateral evidence and do not identify the brain regions of oxidative stress in living patients.

On the basis of these findings from *in vitro* studies, ^{62}Cu-ATSM PET was performed to visualize brain regions of oxidative stress in patients with ALS.[70] In the study, we demonstrated that ALS patients showed greater tracer accumulation in the motor neuron related areas, including the bilateral cortical regions of the right superior parietal lobes, as well as the motor cortex, compared with healthy controls (Figure 3). The results were consistent with findings

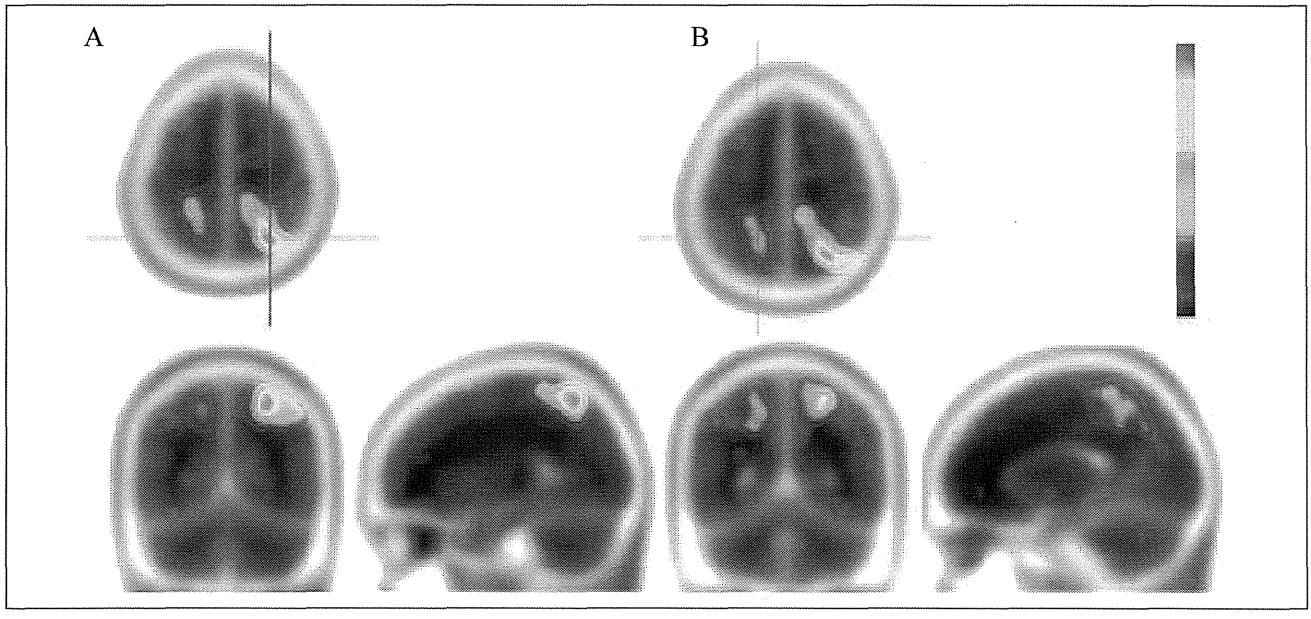

Figure 3.—Enhancement of ^{62}Cu-ATSM accumulation in patients with ALS (N.=12) compared with age-matched healthy controls (N.=10). Bilateral motor neuron-related regions (A, right hemisphere, B, left hemisphere) are presented.

of previous basic studies. Most of the regions with high uptake around the central sulcus may be related to motor neurons because primary motor neurons are considered to be included not only in the precentral gyrus, but also in the postcentral gyrus and paracentral lobule.[71] Furthermore, ^{62}Cu-ATSM accumulation in these regions was well correlated with the clinical severity of the patients evaluated by the ALSFRS-R score. This result suggests that the degree of oxidative stress and mitochondrial dysfunction may be closely associated with the progression of motor neuron degeneration and the severity of disease in the ALS brain.[70] This finding is also in line with a previous ^{18}F-FDG PET study observing changes in glucose metabolism in the brains of ALS patients. Pagani et al. studied FDG-PET in ALS patients to evaluate brain glucose metabolism and demonstrated increased FDG accumulation in the brain stem and hypometabolism in the frontal and occipital cortices.[72, 73] The results suggest that oxidative stress and mitochondrial dysfunction induced neuronal loss and facilitated anaerobic glycolysis, an inefficient pathway of energy metabolism, in the remaining motor-related brain regions which caused a relative increase in glucose consumption.

Recently, molecular imaging for neuroinflammation was applied to the brains of ALS patients. PET scans were performed for patients with sporadic ALS using a radioligand for the imaging of translocator protein (TSPO) to elucidate activated microglia and reactive astrocytes.[74] The study by Corcia *et al.* showed enhanced neuroinflammation in several cortical regions, including the primary motor, supplementary motor, and temporal cortices, at an early stage of the disease. Neuroinflammation induced by oxidative stress may occur concurrently, which encompasses neurodegeneration in the brains of ALS. Furthermore, PET studies using ^{11}C-flumazenil or ^{11}C-WAY100635 showed reduced neuronal density in the frontal and parietal motor cortex and extra-motor areas in ALS patients.[75, 76] In SPECT studies of Parkinson's disease, patients tend to show increased perfusion in the basal ganglia because of their hyper-metabolism,[77] and this may affect the initial uptake of Cu-ATSM. However, motor neuron areas in ALS do not show an increase in blood flow, and thus, the increase in Cu-ATSM uptake seems to simply reflect oxidative stress or mitochondrial dysfunction in the brain region. Considering these results, the increased ^{62}Cu-ATSM uptake in the motor regions may be a good surrogate marker for assessment of ALS severity.

Alzheimer's disease and other dementias

Alzheimer's disease is the predominant clinical and pathological state of dementia and the most common age-related neurodegenerative disorder. Global multi-institutional clinical studies are on going in many countries, as well as local communities. The pathogeny of the disease is assumed to be extracellular aggregated deposits of amyloid-β (Aβ) peptides and neurofibrillary tangles caused by intracellular aggregated tau protein.[78] Thus, various Aβ imaging probes have been developed for imaging of Alzheimer's disease and several promising PET tracers, such as ^{11}C-PiB (Pittsburg compound-B), ^{18}F-flutemetamole and ^{18}F-florbetapir, have already been widely used in clinical studies. Recently, tau-imaging probes were also developed and relevance with pathologic evidence of Alzheimer's disease was reported.[79-81] On the other hand, fibrillar Aβ deposition in the mitochondria, which causes mitochondrial dysfunction, is also reported to play an important role in the pathogenesis of Alzheimer's disease.[78,82-84] Oxidative stress and mitochondrial dysfunction are considered to be major indirect events for hyperphosphorylation of tau protein. However, oxidative stress imaging for Alzheimer's disease, as well as other dementias, has not yet been reported. Investigation of the relationship between progression of disease and state of oxidative damage and/or mitochondrial impaired function would be a good target for future clinical studies.

Conclusions

Mitochondrial dysfunction and accompanying oxidative injury are considered to be major direct or indirect causes in most neurodegenerative diseases.[85] Radioactive copper labeled Cu-ATSM is a promising PET tracer which can delineate information on cerebral oxidative stress and mitochondrial impairment noninvasively in those diseases. Cu-ATSM PET can detect affected brain regions by oxidative stress under over-reductive environment in patients and provide valuable information on the pathogenesis of disease. It may also be useful to monitor and follow-up antioxidant treatment for neurodegenerative disorders associated with oxidative injury in the near future. Selective molecular imaging probes targeting ROS are also expected as a new option for oxidative stress imaging.

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その他の重要な病態　進行性ミオクローヌスてんかんを示す疾患

MERRF(赤色ぼろ線維を伴うミオクローヌスてんかん症候群)

MERRF(myoclonus epilepsy associated with ragged-red fibers)

井川正道[1,2]
米田　誠[3]

Key words：MERRF，ミトコンドリア病，ミトコンドリア遺伝子変異，ミオクローヌス，てんかん，運動失調

1. 概念・定義

MERRF(myoclonus epilepsy associated with ragged-red fibers：福原病)は，ミオクローヌス，てんかん，運動失調，筋力低下，認知症などを主徴とするミトコンドリア脳筋症の一つである[1,2]．MERRFでみられるこれらの症状は，いわゆる進行性ミオクローヌスてんかん(progressive myoclonus epilepsy：PME)と共通するものであるため，本疾患は当初PMEの一つに含められていた．しかし1980年に新潟大学の福原らが，PMEと診断されていた患者の骨格筋にミトコンドリア形態異常である赤色ぼろ線維(ragged-red fibers：RRF)を発見し，これによって本疾患はミトコンドリア異常を病因とする新たな疾患単位と考えられるようになった[1]．さらに1990年に，MERRF患者のミトコンドリア遺伝子(mtDNA)におけるリシン転移RNA(tRNA)領域の点突然変異が，著者ら[3]，およびShoffnerら[4]によって遺伝的病因として発見され，本疾患における疾患概念が確立した．

現在ではMERRFは，慢性進行性外眼筋麻痺(chronic progressive external ophthalmoplegia：CPEO)，MELAS(mitochondrial encephalopathy, myopathy, lactic acidosis and stroke-like episodes)と並んで，ミトコンドリア脳筋症の三大病型の一つとして位置づけられている．

2. 病　　因

mtDNAの変異がMERRFの原因となる．mtDNAのリシンtRNA領域の塩基番号8344における，アデニンからグアニンへの点突然変異(A8344G)が，MERRFにおいて最初に報告された変異であり[3,4]，本変異は典型的な症状を呈するMERRF患者の80％以上に検出される[5]．同じリシンtRNA領域には，T8356C変異，G8363A変異，G8361A変異もMERRFの原因遺伝子として発見されており，本領域に変異の90％が集中している．ごく少数ながらそれ以外の領域にも，G611A変異，G15967A変異などが報告されている．また，通常はMELASの病型をとるはずのA3243G変異もMERRFの原因となることがあるなど，遺伝子変異と病型(表現型)が一致しないこともあるため注意が必要である．現在までの報告例はMITOMAP[http://www.mitomap.org/]で確認することができる．

3. 病　　態

ミトコンドリアは，身体活動に必要なエネルギー産生を行っている細胞内小器官であり，ヒトのほぼすべての細胞に数十個存在している．ATP産生の要である呼吸鎖と，呼吸鎖酵素やtRNAなどのミトコンドリア機能に重要な要素をコードしている独自の遺伝子(mtDNA)をその内部に有している．このため，MERRFのようにmtDNAに変異があると，ミトコンドリア

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