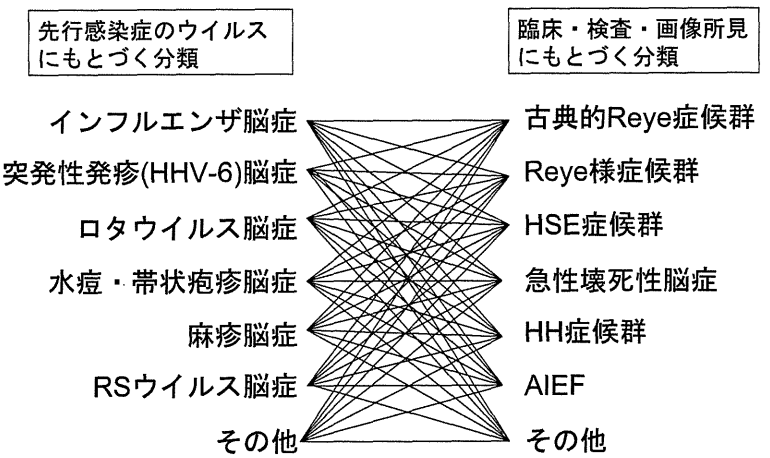

図1　ウイルス性急性脳症の分類

HHV-6：human herpesvisus-6, RS：respiratory syncytial, HSE：hemorrhagic shock and encephalopathy, HH：hemiconvulsion-hemiplegia, AIEF：acute infantile encephalopathy predominantly affecting the frontal lobes（前頭葉を主として障害する乳幼児急性脳症）

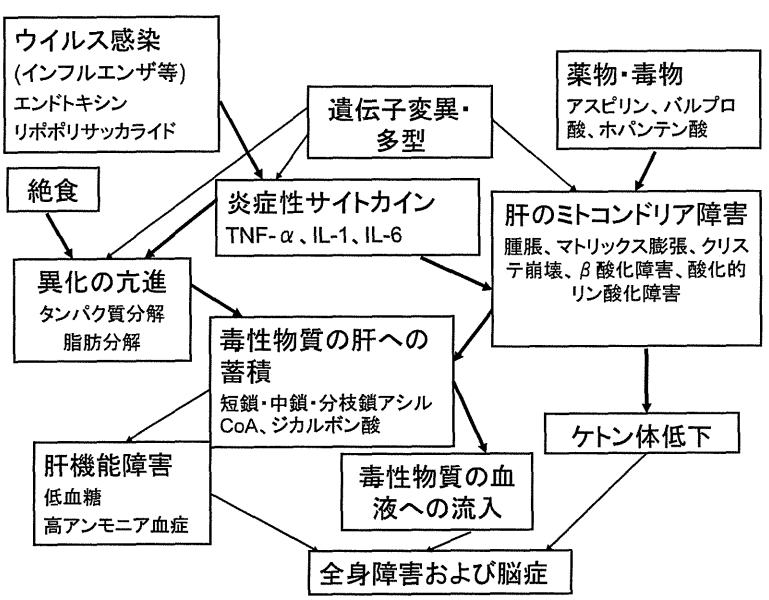

図2　代謝異常による急性脳症（古典的 Reye 症候群）の病態生理（推定）

TNF-α：tumor necrosis factor-alpha, IL-1：interleukin-1, IL-6：interleukin-6.

リア細胞膜にあるエネルギー依存性チャネルの機能不全により細胞内にイオンや水分子が流入する病態である．多くの場合，その背景にはミトコンドリア代謝異常によるエネルギー産生不全があると推測される．血管性浮腫は，血液脳関門（blood-brain barrier）の機能低下による脳血管の透過性亢進であり，血管内皮障害が病態の中心にある[8]．近年，頭部 MRI 拡散強調画像の応用により，細胞性浮腫と血管性浮腫を画像検査で鑑別することも可能となった．

急性脳症の分類

急性脳症には多くの症候群が含まれる．これらの症候群の間には共通点と相違点とがある．

急性脳症の分類には，先行感染の病原ウイルスによる分類と，脳症の臨床病理学的特徴にもとづく症候群分類とがある．両者の間に特異的関係はなく，事実上，どのウイルスがどの症候群を生じることもありうる（図1）．

これらの多くの症候群は，主たる病態により3群に分類される[8]．以下，それぞれの症候群の概要を述べる．

1）代謝異常を主病態とする急性脳症

a）先天代謝異常症

脂肪酸輸送・酸化の障害，有機酸代謝異常症，糖代謝異常症，尿素サイクル異常症などの先天代謝異常症

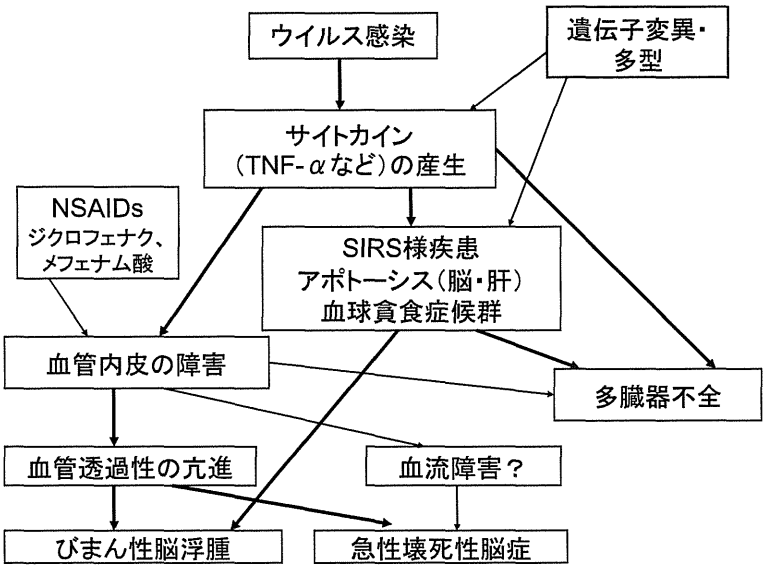

図3　サイトカインストームをともなう急性脳症(Reye 様症候群, hemorrhagic shock and encephalopathy 症候群, 急性壊死性脳症) の病態生理 (推定)
NSAIDs:non-steroidal anti-inflammatory drugs, SIRS:systemic inflammatory response syndrome

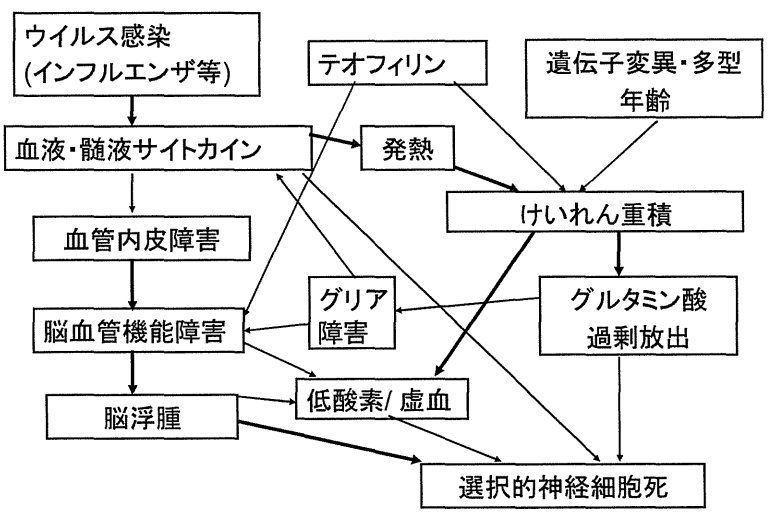

図4　興奮毒性による急性脳症 (けいれん重積型) の病態生理 (推定)

が, 急性脳症様のエピソードとして発症することがある[9]. これらの疾患は, 典型的な症例(酵素活性低下が中等度以上) は慢性進行性の経過を辿るが, 非典型的な症例 (酵素活性低下が軽度) はふだん無症状ないし軽微な症状のみで, 感染症や飢餓を契機に急性発症することがある.

b) 古典的 Reye 症候群

高度の肝障害に続発する急性脳症. びまん性の脳浮腫と肝細胞の脂肪変性 (微細脂肪滴沈着) をきたす. 肝ミトコンドリアの形態・機能が一過性の異常をきたし, 糖・脂肪代謝, 尿素サイクルが正常に作動しなくなり, 低血糖・高脂血症・高アンモニア血症をきたす. ウイルス感染にともなう炎症性サイトカインが病態の上流の主役であり, これに絶食や薬剤 (サリチル酸など) が増悪要因として関与する[10](図2).

2) サイトカインストームを主病態とする急性脳症

a) Reye 様症候群

急性脳腫脹型などと称されることもあり, 定義・名称とも確定していない. 肝障害をともなう急性脳症で, びまん性の血管性脳浮腫をきたす. 高アンモニア血症や低血糖は生じない. インフルエンザ脳症の重症例でよく見られる病型である.

b) hemorrhagic shock and encephalopathy 症候群

顕著な出血傾向とショック (hypovolemic shock) を

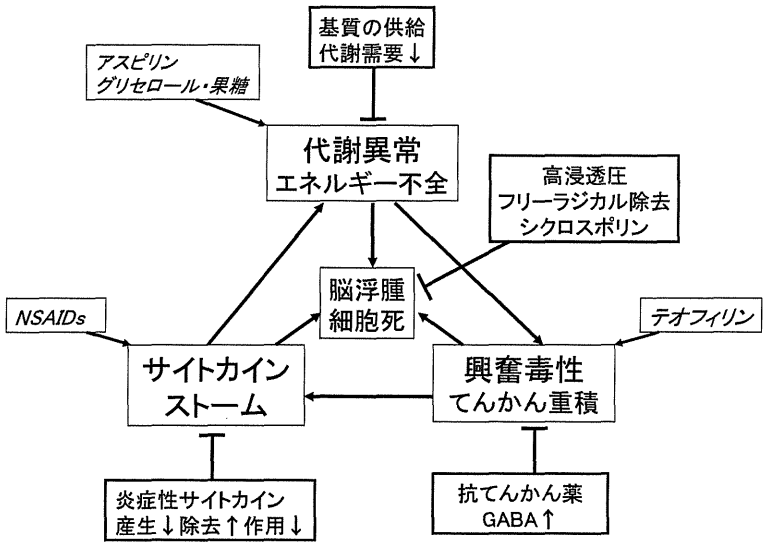

図5　病態の相互関係と治療
病態を増悪しうる薬物を斜字で，治療法を太枠で示した．
GABA：γ-aminobutyric acid（ガンマアミノ酪酸）

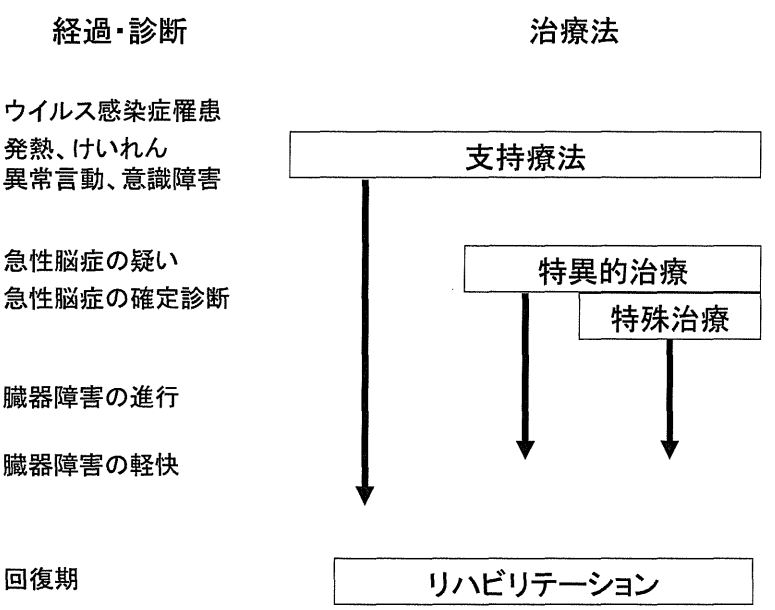

図6　急性脳症の経過・診断と治療法

ともなう急性脳症．大脳皮質全体の浮腫をきたす例が多い．ショック，出血，下痢，乏尿などの臨床症状と血液凝固異常，急性腎不全，高ナトリウム血症などの検査所見が特徴的である[11]．

Reye様症候群やhemorrhagic shock and encephalopathy症候群の頭部CT・MRIでは，全脳ないし大脳皮質全域の浮腫が早発性（発症後48時間以内）に出現する．神経病理学的には脳の血管性浮腫に加え，神経・グリア細胞のアポトーシスとミクログリア活性化が認められる[12]．

c）急性壊死性脳症

びまん性脳浮腫に加え，両側対称性の視床病変をきたす急性脳症．大脳白質や脳幹被蓋，小脳髄質にも病変がしばしば分布する．肝機能障害と髄液蛋白増加が多くの例で見られる．最重症例はショックやDIC，多臓器不全，血球貪食症候群をともなう[13]．

神経病理学的には灰白質・中心部の病変で点状出血と壊死，白質・周辺部の病変で血管性浮腫が見られる[2)13)]．

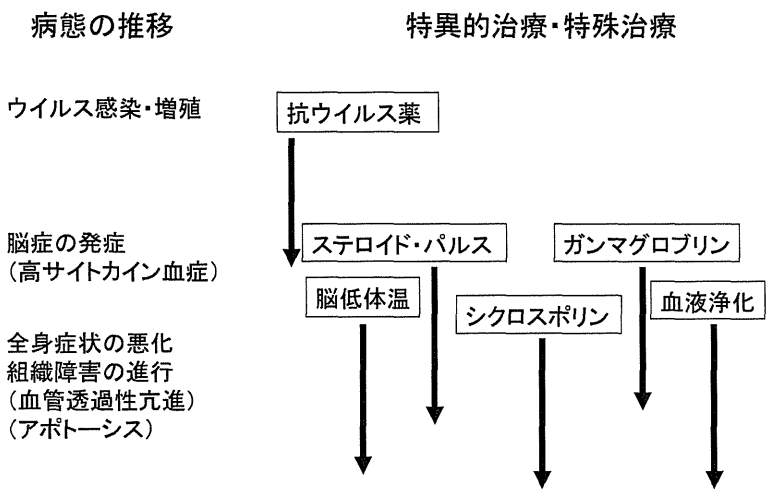

図7　急性脳症の病態の推移と特異的治療・特殊治療

d）病態

Reye 様症候群，hemorrhagic shock and encephalopathy 症候群，急性壊死性脳症ではショック，播種性血管内凝固（DIC），多臓器不全など systemic inflammatory response syndrome（SIRS）の病態を合併しやすい．血液・髄液中の炎症性サイトカインを測定すると上昇しており，とくに血液中のレベルが異常高値である[8)14)]．サイトカインストームによる脳血管透過性の亢進と臓器実質細胞のアポトーシスが病態の中心と推測される（図3）．

3）興奮毒性を主病態とする急性脳症

けいれん重積型急性脳症と称される症候群である[3)]．二相性経過と遅発性拡散低下をともなう急性脳症（acute encephalopathy with biphasic seizures and late reduced diffusion）[4)]，亜急性脳症など，複数の同義・類似の概念がある．

遷延・群発した有熱時けいれん，けいれん後意識障害に続いて，大脳皮質機能低下の症状を呈する．発作とけいれん後意識障害は，典型例では二相性の経過を示す．脳浮腫は通常，大脳皮質に限局し，遅発性（通常，第4〜7病日）に出現する．病変部皮質は急性期（第1病週）には浮腫と血流増加を示すが，亜急性期（第2〜4病週）には萎縮・血流低下をきたす[15)]．病変分布は症例によりさまざまだが，中心前回・後回は障害されにくい[3)16)]．両側前頭葉や一側大脳半球に分布する症例は，下記の症候群に該当する．

a）前頭葉を主として障害する乳幼児急性脳症[17)18)]

失語や自発性低下を呈する．常同運動もしばしば見られる．

b）hemiconvulsion-hemiplegia 症候群[15)19)]

片麻痺と知的障害を呈する．てんかんをしばしばともなう．

c）病態

有熱時けいれん重積にともなうグルタミン酸の過剰な放出がシナプス後神経細胞の選択的・遅発性の細胞死を惹起すると推測されるが，詳細は未解明である[8)20)]（図4）．

治療：総論

1）治療の基礎

前節で述べたように，急性脳症には代謝異常，サイトカインストーム，興奮毒性の3種の病態が関与し，病型（症候群）によって主な病態が異なる．ただし1つの病態が主役であるにしても，他の2つがしばしば脇役を演じている．最重症例では複数の病態が相互に関連して，一種の悪循環を形成しつつ，脳浮腫と細胞死に至っていると推測される（図5）．

代謝異常（エネルギー不全）に対する治療としては，利用可能な基質を供給するとともに，脳細胞の代謝需要を軽減する．増悪要因となりうるサリチル酸などを使用しない．サイトカインストームに対しては，炎症性サイトカイン産生を低下させ，除去を促進し，作用を軽減させる．増悪要因となりうる非ステロイド性抗炎症薬（NSAIDs；ジクロフェナク，メフェナム酸など）を使用しない．興奮毒性（てんかん重積）に対しては抗てんかん薬でてんかん放電を終息させ，脳内ガンマアミノブチル酪酸（GABA，抑制性神経伝達物質）を増やす．増悪要因となりうるテオフィリン製剤を使用しない．進行しつつある脳浮腫に対しては高浸透圧療法を行い，細胞死に対してフリーラジカル除去やシクロスポリン投与を試みる（図5）．

2）治療の実際

インフルエンザ脳症に関しては，厚生労働省の研究班（新興・再興感染症研究，研究代表者：森島恒雄教

授）の編纂によるガイドラインがある．初版[6]は2005年11月，改訂版[7]は2009年9月に刊行された．本ガイドラインの基礎になるエビデンスはあくまで季節性インフルエンザに関するものであり，新型インフルエンザや他のウイルス感染症に関するものではない．

しかし，急性脳症では先行感染の病原ウイルスによる病態の差は小さい（図1）．例えば先行感染がインフルエンザであっても，それ以外の感染症であっても，いったん急性壊死性脳症を発症すれば，所見や経過に差はない[21]．したがってインフルエンザ脳症ガイドラインの治療方針を，他のウイルス性急性脳症にも適用することはじゅうぶん可能と推測される．

急性脳症の治療の基本は支持療法である．支持療法はけいれん，異常言動，意識障害など脳症の初期症状が出現した段階，診断が未確定の時点で開始され，その後の診断確定，病状の進行に応じて強化される．急性脳症の疑い診断の段階では，鑑別診断を進めながら，症例の重症度，進行の速度を勘案しつつ，特異的治療の開始を考慮する．臓器障害の進行が急速かつ重篤な症例では，特殊治療を追加する（図6）．

治療：各論

インフルエンザ脳症ガイドライン[7]に準拠しながら，一部を改変して，要点を述べる．病態の推移に応じて各治療法を選択し，組み合わせる（図7）．

1）支持療法

支持療法は非特異的治療であり，急性脳症の病態の進行を直接阻止するものではない．しかし急性脳症の経過中には低酸素・虚血・低血糖などによる二次性脳損傷が生じやすく，これを防ぐことは重要である．

忘れてはならないのは，サイトカインストーム型など重症の病型は，「脳症」という病名にかかわらず全身疾患であるという事実である．当然，全身管理が不可欠である．

a）心肺機能の評価と安定化

来院時に初期蘇生が必要な際は，PALS2005に準じて行う．意識レベル，気道・呼吸・循環の状態を評価する．必要に応じ酸素投与を開始し，モニターを装着する．気道を確保する．気管挿管は，意識レベルがGlasgow Coma Scaleで8点以下，Japan Coma Scale でII-30以上の際に考慮する．呼吸管理は経皮酸素分圧95%以上，血中二酸化炭素分圧35～45mmHgを目標として行う．循環管理の基本は循環血漿量の確保とショックの認識・治療である．細胞外液型の輸液製剤を用いる．水は必要水分量を投与する．電解質管理では，治療的高ナトリウム血症（150～160mEq/L）の導入を考慮する．血糖値は100～150mg/Lを目標とする．

b）中枢神経の管理

意識レベル・瞳孔・けいれんについて評価する．けいれんの管理はけいれん遷延状態（5分以上）・けいれん重積状態（30分以上）・難治性けいれん重積状態（抗てんかん薬静注に抵抗）などの状態を区別し，それぞれに応じて治療を行う．治療は迅速に開始すべきで，重積状態では設備とスタッフが整っていることが望ましい．

けいれん遷延状態では抗てんかん薬の非経静脈的投与も選択しうるが，けいれん重積状態では第1選択としてジアゼパムまたはミダゾラムの静注，第2選択としてフェノバルビタールまたはフェニトインの静注を行う．ミダゾラム持続静注により意識状態の評価が不確実となるため，急性脳症の確定診断を遅らせるデメリットを考慮にいれたうえで適応を決定すべきである．

難治性けいれん重積状態ではミダゾラムまたはチオペンタールを静注する．

頭蓋内圧亢進の管理には，D-マンニトールを静注する．急性脳症が疑われる文脈では，グリセロール製剤は推奨しない．これは一部の代謝異常症（フルクトース1,6-ビスフォスファターゼ欠損症，シトリン欠損症）を増悪する可能性が憂慮されるからである．

c）体温の管理

40℃を超える高体温に対しては，アイスパック，送風，冷拭により積極的に解熱する．解熱薬としてはアセトアミノフェンを使用し，アスピリンやNSAIDs（上記）は用いない．

d）高次医療機関への搬送

2）特異的治療

a）メチルプレドニゾロン・パルス療法

期待される効果は，脳においては脳浮腫軽減と脳内サイトカイン産生抑制，全身においては高サイトカイン血症の軽減と合併する病態（血球貪食症候群など）の治療である．適応は急性脳症の種々の病型，とくにサイトカインストームをともなう症候群である．方法として，メチルプレドニゾロン30mg/kg/日の点滴静注を3日間行う．ヘパリン持続点滴を併用する．副作用は高血圧，高血糖，眼圧上昇，その他である．

インフルエンザ脳症におけるパルス療法の効果は，エビデンスレベルIII-Aである．発症1日目に投与開始すると予後良好な傾向があると報告された[22]．急性壊死性脳症におけるステロイド療法（デキサメサゾン静注をも含む）の効果は，脳幹・小脳病変がない症例で発症24時間以内に投与開始した場合，有意に予後の良いことが報告された[23]．

b）ガンマグロブリン大量静注療法

期待される効果は，全身的な高サイトカイン血症の

改善である．適応は急性脳症のうち，とくにサイトカインストームをともなう病型である．方法は静注用ガンマグロブリン1g/kgを10〜15時間で点滴静注する．副作用のうちでは，アナフィラキシーに最も警戒を要する．急性脳症に対する効果について，じゅうぶんなエビデンスは得られていない．急性壊死性脳症では有意差が見られなかった[23]．

3）特殊治療

a）脳低体温療法

期待される効果は，脳においては脳内サイトカイン産生抑制，脳浮腫軽減，そして脳保護作用，全身においては高サイトカイン血症の軽減である．適応は急性脳症の重症例であり，興奮毒性による急性脳症（けいれん重積型）に対しても，一部の施設で積極的に適用されている．方法はブランケット冷却加温システムを用いて体温を33〜35℃に下げ，約48時間維持する．脳圧モニターが望ましい．鎮静・筋弛緩を併用する．復温は0.5℃/12時間の速度で緩徐に行う．急性脳症に対する効果に関し，十分なエビデンスは得られていない．しかし複数の施設で本療法を導入した後，導入前にくらべ治療成績が向上したという報告・情報はしばしば聞かれる[24]．

b）血液浄化療法

期待される効果は，炎症性サイトカインや他の生理活性物質の血液からの除去である．適応は急性脳症のうち，サイトカインストームをともなう重症例である．血清アスパラギン酸アミノトランスフェラーゼ（AST），乳酸デヒドロゲナーゼ（LDH），フィブリン・フィブリノゲン分解産物（FDP），Dダイマーの上昇が適応の基準となりうる．方法は血漿交換または持続的血液濾過透析（CHDF）のいずれかによる．血液浄化療法は設備と技術を要し，侵襲もあるので従来の適用例は重症例に限られていた．このためその有効性について，じゅうぶんなエビデンスは得られていない．しかし症例報告では劇的な奏功例があるようだ[25]．

c）シクロスポリン療法

期待される効果はアポトーシスの抑制と組織障害の軽減である（図6）．適応は急性脳症のうち，とくに多臓器不全が進行中の症例である．血清AST，LDH，クレアチンキナーゼ（CK），ミトコンドリアASTの上昇が適応の基準となりうる．方法は，シクロスポリン1〜2mg/kg/日の持続点的静注を7日間続けるという，簡便なものである．有効性について，じゅうぶんなエビデンスは得られていない[26]．

d）エダラボン療法

期待される効果はフリーラジカルの除去，酸化ストレスの軽減である．適応は，急性脳症のさまざまな病型（けいれん重積型を含む）について考慮される．方法は，エダラボン0.5mg/kg/日を1日2回静注するというもので，簡便かつ安全である[27]．急性脳症における有効性については，エビデンスが乏しい．

治療の現状と問題点

1）病態と治療

先に述べたように，急性脳症のさまざまな病型には共通点と相違点がある．したがって治療法にも共通のものと個別のものがあってよいはずである．しかし現実には，前節の特異的治療・特殊治療の多くがサイトカインストームに対する治療法であり，興奮毒性（けいれん重積型）に対する治療法は乏しい．脳低体温療法が期待を集めているがまだエビデンスは乏しく，シクロスポリンやエダラボンについてはほとんど未知数である．代謝異常に関しても，特異的治療法のレパートリーは小さい．

サイトカインストームに対抗する治療法は多々あるが，それらの適応基準は確立していない．有効性が証明されたのは，ステロイド療法のみである．ステロイドといえども，劇症の経過をたどる症例（急性壊死性脳症の一部など）では診断時，すでに手遅れの場合がよくある．

2）治療研究の困難さ

急性脳症の多くの症候群が提唱・確立されたのは1993年以降であり，疾患概念は新しく，知見の蓄積は乏しい．罹病率は高くなく，施設ごとの症例数は少ない．複数の症候群があるうえ，同じ病型でも症例ごとの重症度はさまざまである．治療開始時点における予後は予測しがたい．現場では複数の治療法が同時に施行され，個別の治療効果の判定はむずかしい．急性発症し，急激な経過をたどり，早期診断は困難である．その結果，病態の把握がふじゅうぶんなまま治療開始せざるを得ないことが多い．治療法の無作為割り付けや二重盲検は倫理的・技術的に不可能である．

このように急性脳症には治療研究を困難にする多数の要因がある．

3）死亡率の低下

このような困難にもかかわらず，1998年以降今日まで，インフルエンザ脳症の死亡率は一貫して低下してきている．厚生労働科学研究・森島班のデータによると2000年以前は約30%であったが，2007年以降は8%前後である．死亡率低下の原因は病型別頻度の変化（死亡率の低いけいれん重積型の比率が増加した），症例登録の変化（軽症例が登録されやすくなった）など複数あると推測されるが，治療法の進歩（特異的治療・特殊治療の採用）も寄与していることは疑いない．

4）今後の課題

改善したとはいえ，死亡率8%は決して満足すべき

数字ではない．また現時点で，生存者の多く（20～30%）に神経学的後遺症（知的障害，高次脳機能障害，運動麻痺，てんかんなど）が残っている．

治療成績をさらに向上させるには，診断の進歩も必要である．とりわけ早期診断用のバイオマーカー，重症度判定用の指標，病勢・治療効果の指標を開発・考案することが喫緊の課題である．

文　献

1) Mizuguchi M. Acute encephalopathy with necrosis of bilateral thalami. Clinical aspects. Neuropathology 1993；13：327—331.
2) Mizuguchi M, Abe J, Mikkaichi K, et al. Acute necrotising encephalopathy of childhood：a new syndrome presenting with multifocal, symmetric brain lesions. J Neurol Neurosurg Psychiatry 1995；58：555—561.
3) 塩見正司．インフルエンザ脳症—臨床病型分類の試み—．小児科臨床　2000；53：1739—1746.
4) Takanashi J, Oba H, Barkovich AJ, et al. Diffusion MRI abnormalities after prolonged febrile seizures with encephalopathy. Neurology 2006；66：1304—1309.
5) Tada H, Takanashi J, Barkovich AJ, et al. Clinically mild encephalitis/encephalopathy with a reversible splenial lesion. Neurology 2004；63：1854—1858.
6) 厚生労働省インフルエンザ脳症研究班．インフルエンザ脳症ガイドライン．小児科臨床　2006；59：339—364.
7) 厚生労働省インフルエンザ脳症研究班．インフルエンザ脳症ガイドライン［改訂版］．小児科臨床　2009；62：2483—2528.
8) Mizuguchi M, Yamanouchi H, Ichiyama T, et al. Acute encephalopathy associated with influenza and other viral infections. Acta Neurol Scand 2007；115：S45—56.
9) Purevsuren J, Hasegawa Y, Kobayashi H, et al. Urinary organic metabolite screening of children with influenza-associated encephalopathy for inborn errors of metabolism using GC/MS. Brain Dev 2008；30：520—526.
10) Visentin M, Salmona M, Tacconi MT. Reye's and Reye-like syndromes, drug-related diseases? (causative agents, etiology, pathogenesis, and therapeutic approaches). Drug Metab Rev 1995；27：517—539.
11) Chaves-Carballo E, Montes JE, Nelson WB, et al. Hemorrhagic shock and encephalopathy：Clinical definition of a catastrophic syndrome in infants. Am J Dis Child 1990；144：1079—1082.
12) Nakai Y, Itoh M, Mizuguchi M, et al. Apoptosis and microglial activation in influenza encephalopathy. Acta Neuropathol 2003；105：233—239.
13) Mizuguchi M. Acute necrotizing encephalopathy of childhood：a novel form of acute encephalopathy prevalent in Japan and Taiwan. Brain Dev 1997；19：81—92.
14) Ichiyama T, Isumi H, Ozawa H, et al. Cerebrospinal fluid and serum levels of cytokines and soluble tumor necrosis factor receptor in influenza virus-associated encephalopathy. Scand J Infect Dis 2003；35：59—61.
15) 田中佳子，中西洋子，浜野晋一郎，他．急性小児片麻痺における脳血流シンチグラフィーの経時的変化について．脳と発達　1994；26：68—73.
16) 塩見正司．テオフィリンは治療域濃度であっても，けいれん重積型急性脳症の原因となる．小児科臨床　2006；59：187—196.
17) Yamanouchi H, Kawaguchi N, Mori M, et al. Acute infantile encephalopathy predominantly affecting the frontal lobes. Pediatr Neurol 2006；34：93—100.
18) Yamanouchi H, Mizuguchi M. Acute infantile encephalopathy predominantly affecting the frontal lobes (AIEF)：A novel clinical category and its tentative diagnostic criteria. Epilepsy Res 2006；70：S263—268.
19) Gastaut H, Poirier F, Payan H, et al. H.H.E. syndrome；hemiconvulsions, hemiplegia, epilepsy. Epilepsia Eksp Khirurg 1960；1：418—447.
20) Takanashi J, Tada H, Terada H, et al. Excitotoxicity in acute encephalopathy with biphasic seizures and late reduced diffusion. Am J Neuroradiol 2009；30：132—135.
21) Okumura A, Abe S, Kidokoro H, et al. Acute necrotizing encephalopathy：a comparison between influenza and non-influenza cases. Microbiol Immunol 2009；53：277—280.
22) 小林慈典，富樫武弘，水口　雅，他．インフルエンザ脳症特殊治療の全国調査．日児誌　2007；111：659—665.
23) Okumura A, Mizuguchi M, Kidokoro H, et al. Outcome of acute necrotizing encephalopathy in relation to treatment with corticosteroids and gammaglobulin. Brain Dev 2009；31：221—227.
24) 宮本健志，三井昌彦，片塩　仁，他．脳低体温療法とステロイドパルス療法が奏効したtheophylline関連けいれん重積症の1例．脳と発達　2006；38：219—220.
25) 池田裕一，赤城邦彦，高橋英彦，他．肝障害，腎不全合併の急性壊死性脳症患児への持続血液濾過透析療法．日児誌　2002；106：81—84.
26) 鍵本聖一．インフルエンザ脳症に対する治療戦略について—インフルエンザ脳症ガイドライン改訂版におけるインフルエンザ脳症に対する支持療法と特殊療法；その背景—．小児科臨床　2010；63：521—526.
27) 田中　学，浜野晋一郎，吉成　聡，他．小児8例におけるエダラボンの使用経験．小児科臨床　2007；60：273—276.

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Differences in the time course of splenial and white matter lesions in clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS)

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ABSTRACT

Two patients with clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) exhibiting lesions in the white matter and entire corpus callosum (type 2) are reported. The time course differed between the splenial lesion and other lesions in the white matter and corpus callosum other than the splenium; the latter disappeared earlier than the former. These findings strongly suggest that MERS type 2 resolves completely through MERS type 1 exhibiting an isolated splenial lesion, and MERS types 1 and 2 have the same pathophysiology. The possible prior white matter lesions in patients with MERS type 1 may explain the neurological symptoms or EEG abnormalities.

1. Introduction

The MR imaging finding of a reversible isolated lesion with transiently reduced diffusion in the splenium of the corpus callosum (SCC) has been reported in patients with clinically mild encephalitis/encephalopathy, leading to a new clinical–radiological syndrome, clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) [1–3]. Reversible lesions with transiently reduced diffusion have also been found with lateral extension from the splenium into the subcortical white matter [4], and with anterior extension involving the entire corpus callosum [5]. Because of the clinical and radiological similarities, we have suggested that these comprise a clinico-radiological spectrum (MERS spectrum), type 1 with an isolated SCC lesion and type 2 with extensive white matter and/or entire callosal lesions. We herein report two patients with MERS in whom MRI on admission revealed type 2 lesions, but on the next day revealed an isolated SCC lesion (type 1), the other lesions having greatly decreased in size and signal intensity, which suggests that MERS type 2 resolves completely through MERS type 1.

2. Case report

2.1. Patient 1

A previously healthy 10-year-old boy was admitted because of recurrent seizures after a 3-day prodromal high fever, which were stopped by intravenous administration of mitazolam. There was no family history or past history of neurological disorders, including epilepsy and developmental retardation. Afterwards, he was drowsy for around 24 h, leading to a clinical diagnosis of acute encephalopathy. The results of neurological examination were unremarkable except for his consciousness level and a positive extensor plantar response. Routine laboratory examination showed a slightly increased C-reactive protein level (0.53 mg/dl) and hyponatremia (Na 131 mEq/l). Cerebrospinal fluid (CFS) examinations revealed normal cell counts, and protein and glucose levels. He was treated with a steroid, acyclovir, and became alert on day 5. Diffusion-weighted images (DWI) on admission (day 4) showed markedly hyperintense lesions in the bilateral white matter and entire corpus callosum with a reduced apparent diffusion coefficient (ADC) (Fig. 1A, B). Second DWI on day 5 showed a markedly hyperintense lesion in the SCC (Fig. 1C), but the lesions in the white matter and corpus callosum other than the SCC had decreased in size and signal intensity (Fig. 1D). Third DWI on day 17 showed the complete resolution of these lesions (Fig. 1E, F). Electroencephalography (EEG) on day 11 showed bilateral occipital slow waves, but no follow-up study was performed. A diagnosis of

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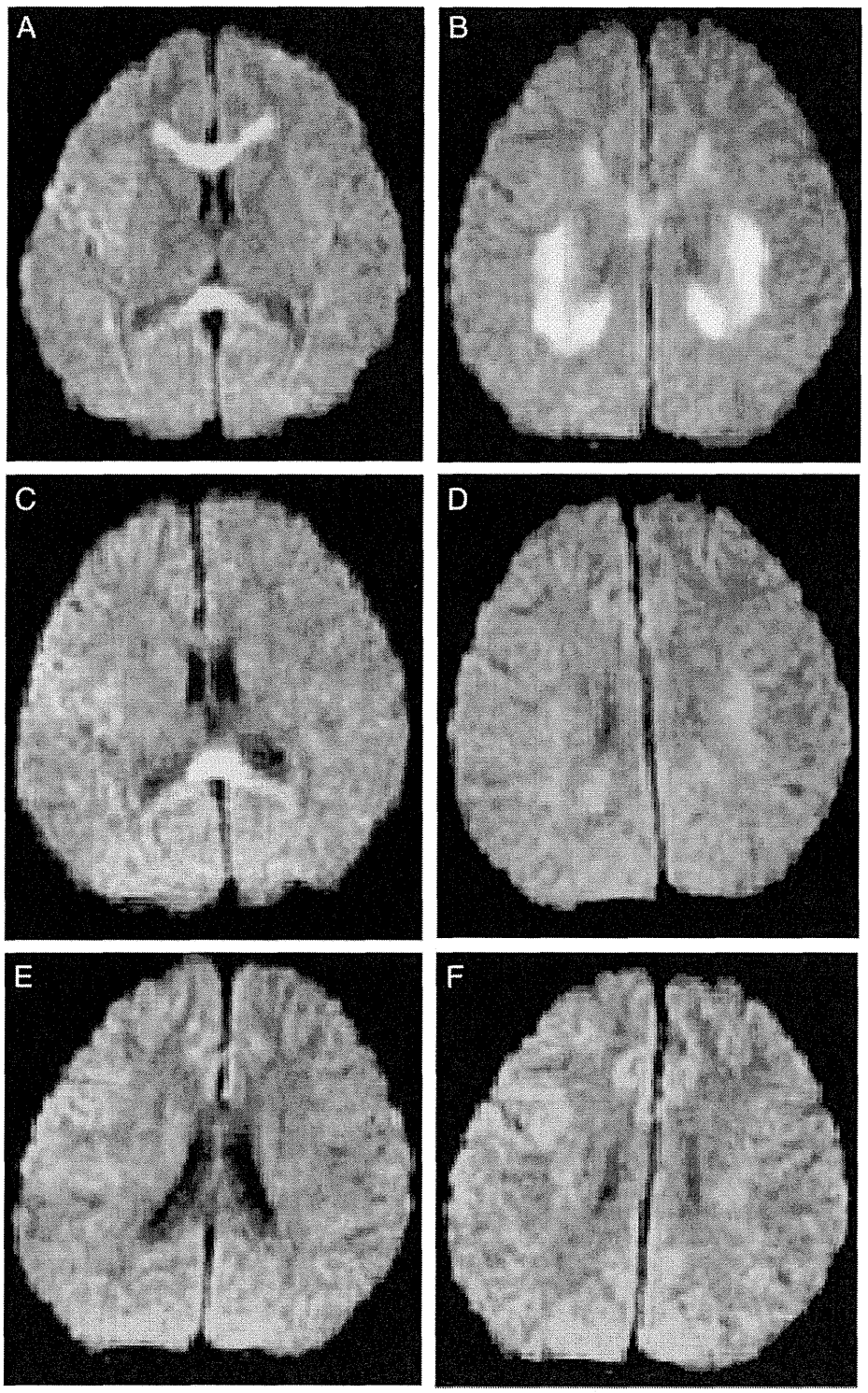

Fig. 1. DWI on admission (day 4) showed markedly hyperintense lesions in the bilateral white matter and entire corpus callosum (A, B). Second DWI on day 5 showed a markedly hyperintense lesion in the SCC (C), but lesions in the white matter and corpus callosum other than the SCC had decreased in size and signal intensity (D). Third DWI on day 17 showed complete resolution of these lesions (E, F).

MERS (type 2) was retrospectively made based on the clinical and radiological features.

2.2. Patient 2

A previously healthy 6-year-old Japanese girl was admitted with recurrent delirious behavior and consciousness disturbance, following a 1-day prodromal fever, cough, and rhinorrhea. Before admission, she had received zanamivir hydrate and acetaminophen based on the diagnosis of influenza A with a positive rapid antigen-detection assay result. There was no family history or past history of neurological disorders, including epilepsy and developmental retardation. On admission (day 2), she was drowsy and presented with recurrent delirious behavior, such as laughter and dancing, but the results of neurological examination were unremarkable. Blood examination revealed an increased white blood cell count (13.300/μl), an increased C-reactive

protein level (5.8 mg/dl), and hyponatremia (Na, 127 mEq/1), but normal levels of ammonia and glucose. CSF examination showed normal cell counts, and protein and glucose levels. EEG on day 1 showed bilateral occipital high voltage slow waves, which had normalized on day 5. She was treated with zanamivir hydrate, and her clinical manifestations improved and completely recovered within 24 h (day 3). MR imaging on admission (day 2) revealed lesions in the diffuse white matter and entire corpus callosum with marked hyperintensity on DWI with a homogenously reduced ADC (Fig. 2A). Second DWI on day 3 showed a markedly hyperintense lesion only in the SCC (Fig. 2B), and mildly hyperintense lesions in the white matter and corpus callosum other than the SCC, which had completely resolved on day 6 (Fig. 2C). A diagnosis of MERS (type 2) was made based on the clinical and radiological features.

3. Discussion

The most important finding in our two patients is that the time course differed between a lesion in the SCC and lesions in the white matter and corpus callosum other than the SCC; the latter disappeared earlier than the former. Only one patient with clinically mild encephalopathy exhibiting the same longitudinal MRI changes has been reported [6]. MRI of the patient on admission showed extensive lesions in the white matter and entire corpus callosum with homogenously reduced diffusion (type 2); a follow-up study after 60 h revealed an isolated SCC lesion (type 1) with no lesions in the white matter or corpus callosum other than the SCC [6]. Our two patients and the previously reported one suggest that type 2 lesions resolve through a period with a type 1 lesion (isolated SCC lesion) within a few days, finally complete resolution; and strongly support the hypothesis that types 1 and 2 have the same pathophysiology.

Among the 54 patients with MERS previously reported, 40 were classified as MERS type 1 with an isolated SCC lesion, and the other 14 as MERS type 2, i.e., 3 patients with lesions in the splenium plus genu, 2 with ones in the entire corpus callosum, and 9 with ones in both the corpus callosum and symmetrical white matter [1]. Among the 14 patients with MERS type 2, there were none in whom MRI showed a longitudinal change from type 2 to type 1, and finally complete resolution. The interval between the initial and follow-up MRI in the 14 patients with MERS type 2 was more than 4 days, during which all the lesions might have disappeared. Follow-up MRI within a few days may have revealed a longitudinal change from type 2 to type 1. Among the 40 patients with MERS type 1, it is reasonable to consider that some had had lesions in the white matter and/or entire corpus callosum prior to the initial MR study.

The most common neurological symptom of MERS is delirious behavior in 54% (29/54), as observed in patient 2, followed by consciousness disturbance in 35%, and seizures in 33%, all of which completely disappear within a month [1,7]. No clinical difference between types 1 and 2 has been reported. Though the pathophysiology of delirium is poorly understood, delirium is more likely to involve both cerebral hemispheres than the hemisphere on one side or the brainstem alone [8]. Neuroimaging and neuropsychological studies have revealed generalized disruption of higher cortical functions in adults with delirious behavior [9]. Therefore, lesions in the bilateral white matter and corpus callosum seen in patients with MERS type 2 may result in disconnection of the bilateral cerebral hemispheres, leading to disruption of higher cortical function, and finally delirium. If patients with type 1 MERS have prior white matter lesions, or have white matter involvement too faint to be detected on routine DWI, that would also explain the neurological symptoms, including delirium. An EEG abnormality has been found in around half of the patients with MERS (21/39 patients), including diffuse slow waves in 17 patients, occipital slow waves in four (as observed in the present two patients), and paroxysmal discharges in two [1]. Almost all the EEG abnormalities normalized on the follow-up study. Transient involvement of the bilateral white matter in MERS may result in disruption of higher cortical function, also leading to transient slow waves on EEG.

The reason for the transiently reduced diffusion within the lesions, and that for the longitudinal difference in the lesions are unknown; we have suggested transient development of intramyelinic edema due to separation of the myelin layers as a possible mechanism [1,2]. A reversible SCC lesion with transiently reduced diffusion, however, has been reported in a 12-day-old neonate [10]. At that age, the SCC is still completely unmyelinated; therefore, another mechanism must be responsible for the reversible SCC lesion in at least some cases. Laboratory evaluation revealed that hyponatremia is common in patients with MERS [11], as observed in the present two patients. Hypotonic hyponatremia results in entry of water into the brain, resulting in cerebral edema. As the axons in the SCC are very tightly packed, it is possible that interstitial edema (water situated between the unmyelinated axons) could have reduced diffusion. The lesions in the white matter, however, cannot be explained by this hypothesis, because interstitial edema in the white matter usually causes increased diffusion. Another possible explanation is the development of a transient inflammatory infiltrate, which might cause reduced

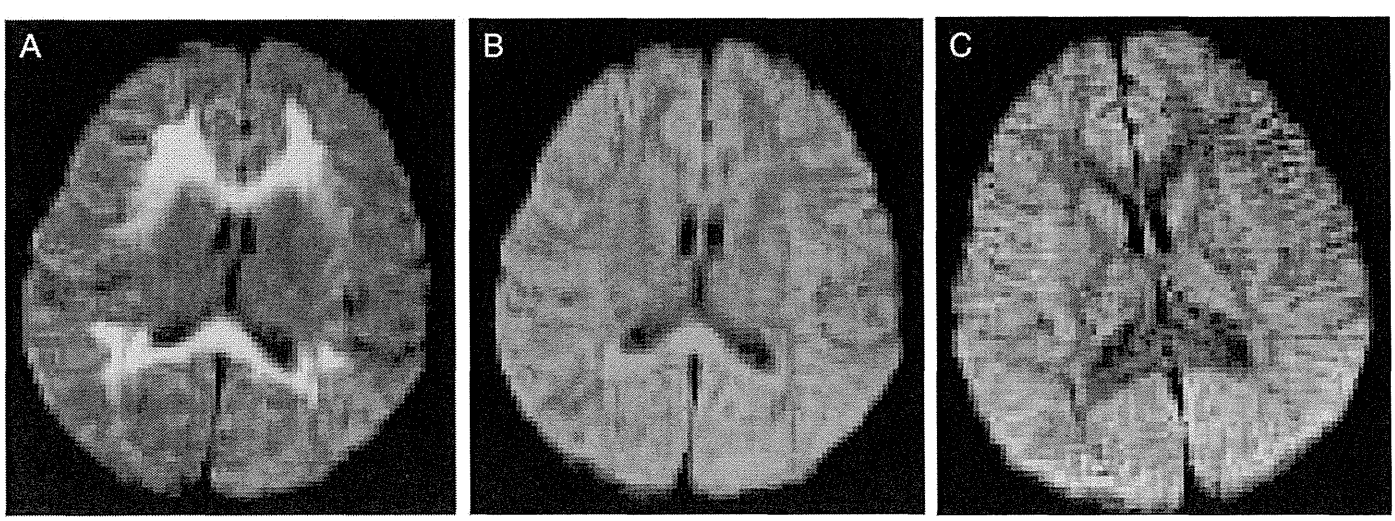

Fig. 2. MR imaging of patient 2. MR imaging on admission (day 2) revealed lesions in the diffuse white matter and entire corpus callosum with marked hyperintensity on DWI (A). Second DWI on day 3 showed a markedly hyperintense lesion only in the SCC (B), which had completely resolved on day 6 (C).

diffusion, as observed in multiple sclerosis. These speculation, however, do not explain why the SCC is specifically involved, why the SCC is involved longer than the white matter or corpus callosum other than the SCC, or why the cerebellar white matter is not affected. Recently, some familial patients with MERS were reported, suggesting a genetic factor might be involved in at least some patients [12]. Further clinical, radiological and genetic studies are, of course, necessary for a definite conclusion.

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References

[1] Takanashi J. Two newly proposed encephalitis/encephalopathy syndromes. Brain Dev 2009;31:521–8.
[2] Tada H, Takanashi J, Barkovich AJ, Oba H, Maeda M, Tsukahara H, et al. Clinically mild encephalitis/encephalopathy with a reversible splenial lesion. Neurology 2004;63:1854–8.
[3] Takanashi J, Barkovich AJ, Yamaguchi K, Kohno Y. Influenza-associated encephalitis/encephalopathy with a reversible lesion in the splenium of the corpus callosum: a case report and literature review. AJNR Am J Neuroradiol 2004;25:798–802.
[4] Takanashi J, Barkovich AJ, Shiihara T, Tada H, Kawatani M, Tsukahara H, et al. Widening spectrum of a reversible splenial lesion with transiently reduced diffusion. AJNR Am J Neuroradiol 2006;27:836–8.
[5] Takanashi J, Hirasawa K, Tada H. Reversible restricted diffusion of entire corpus callosum. J Neurol Sci 2006;247:101–4.
[6] Okumura A, Noda E, Ikuta T, Natsume J, Nagai T, Gotoh Y, et al. Transient encephalopathy with reversible white matter lesions in children. Neuropediatrics 2006;37:159–62.
[7] Takanashi J, Tada H, Kuroki H, Barkovich AJ. Delirious behavior in influenza is associated with a reversible splenial lesion. Brain Dev 2009;31:423–6.
[8] Taylor DA, Ashwal S. Impairment of consciousness and coma 4th ed. In: Swaiman KF, Ashwal S, Ferriero DM, editors. Pediatric neurology: principles & practice. Philadelphia: Mosby Elsevier; 2006. p. 1377–400.
[9] Inouye SK. Delirium in older persons. N Engl J Med 2006;354:1157–65.
[10] Takanashi J, Maeda M, Hayashi M. A neonate showing a reversible splenial lesion. Arch Neurol 2005;62:1481–2.
[11] Takanashi J, Tada H, Maeda M, Suzuki M, Terada H, Barkovich AJ. Encephalopathy with a reversible splenial lesion is associated with hyponatremia. Brain Dev 2009;31:217–20.
[12] Imamura T, Takanashi J, Yasugi J, Terada H, Nishimura A. Sisters with clinically mild encephalopathy with a reversible splenial lesion (MERS)-like features; familial MERS? J Neurol Sci 2010;290:153–6.

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Original article

Carnitine palmitoyl transferase II polymorphism is associated with multiple syndromes of acute encephalopathy with various infectious diseases

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Abstract

The high incidence of acute encephalopathy in East Asia suggests the role of genetic factors in its pathogenesis. It has recently been reported that variations of the *CPT II* (carnitine palmitoyl transferase II) gene may be associated with fatal or severe cases of influenza-associated encephalopathy. In the present study, we examined the genotype of *CPT II* in cases of acute encephalopathy associated with various preceding infections. Twenty-nine Japanese patients with acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) or acute necrotizing encephalopathy (ANE) were studied. The frequency of F352C of *CPT II* exon 4 was significantly higher in patients than in controls. All patients who had allele C in F352C had allele I in V368I and allele M in M647V (CIM haplotype), which reportedly decreases CPT II activity to one third of that with FIM or FVM haplotype. The frequency of CIM haplotype was significantly different between patients and controls, but not between AESD and ANE. Our results revealed that having at least one CIM allele is a risk factor for the onset of acute encephalopathy, regardless of its antecedent infections.

Keywords: Acute necrotizing encephalopathy; Acute encephalopathy with biphasic seizures and late reduced diffusion; Carnitine palmitoyltransferase II; Single nucleotide polymorphism

1. Introduction

Acute encephalopathy is an acute brain dysfunction which usually occurs at the early stage of infectious diseases with high fever. Its main symptoms are impaired consciousness and signs of increased intracranial pressure, often accompanied by convulsions or seizures. Its incidence is highest in infancy and early childhood [1]. Acute encephalopathy consists of several different syndromes. In some syndromes, such as acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) and acute necrotizing encephalopathy (ANE) [2,3], the diagnosis is made easily for most

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patients, whereas in other syndromes, the diagnostic criteria are less clear cut.

The antecedent infection of acute encephalopathy is viral, such as influenza [4] and exanthema subitum [5], in the majority of cases. There is no specific relationship between the viruses and the types of encephalopathy, suggesting that the pathogenesis of acute encephalopathy is mediated primarily by host factors. Moreover, the incidence of acute encephalopathy is higher in East Asians than in Caucasians, implying a role of genetic factors [1].

It has recently been reported that genotypic variants of the carnitine palmitoyl transferase II *(CPT II)* gene are associated with fatal or severe cases of influenza-associated encephalopathy [6]. CPT II is an enzyme localized on the mitochondrial inner membrane, and removes fatty acids from carnitine [7]. Mutations of the *CPT II* gene cause CPT II deficiency, an inborn metabolic error affecting mitochondrial fatty acid β oxidation. When patients with CPT II deficiency are infected with viruses, some develop energy failure, and show a clinical course resembling that of acute encephalopathy [8].

It has recently been reported that thermolabile phenotype variations, formed by single nucleotide polymorphisms (SNPs) of the *CPT II* exon 4 [1055T > G/F352C and 1102G > A/V368I] and exon 5 [1939A > G/M647V] produce thermolabile phenotypes [6]. These variations cause a severe reduction of CPT II activity at high body temperature, although this reduction is minimal or mild at normal body temperature.

In the previous study [6], the subjects were limited to severe cases of acute encephalopathy associated with influenza. In the present study, we conducted a single nucleotide polymorphisms (SNPs) analysis of *CPT II* in patients with acute encephalopathy, including those following antecedent infections other than influenza, and those with a better prognosis. We focused on cases of AESD and ANE in which a diagnosis was definitely made.

2. Materials

2.1. Patients

We recruited patients with AESD and ANE from hospitals in the Kanto District, Japan. In this study, we regarded AESD as synonymous with acute encephalopathy with febrile convulsive status epilepticus (AEFCSE) [1]. Of the various syndromes of acute encephalopathy, we selected AESD (or AEFCSE) and ANE because concrete diagnostic criteria are available [3,9]. In total, twenty-nine patients, nineteen with AESD and ten with ANE, participated in this study. All the patients were Japanese, aged from 8 months to 8 years and 5 months. About 80% of patients were under 2 years of age. Nineteen patients were female, and ten were male. Pathogens of antecedent infections included human herpes virus 6 (HHV6), influenza virus, respiratory syncytial (RS) virus, rotavirus, adenovirus and mycoplasma. The most frequent virus was HHV6 (8 cases), followed by influenza virus (4 cases). The preceding pathogens were not identified in 11 cases (Table 1). We obtained written informed consent from the parents of the patients. This study was approved by the Ethics Committee of the University of Tokyo.

2.2. Controls

We also analyzed the *CPT II* genotype of control subjects, consisting of 100 healthy Japanese adults, 50 male and 50 female, at 20–69 years of age. Purified DNA from controls was extracted from PSC (Pharma SNP Consortium) B cell lines, and supplied by the Human Science Research Resources Bank.

3. Methods

3.1. CPT II genotyping

Peripheral blood samples were collected from the patients. Genomic DNA was extracted from the blood using standard protocols. PCR amplification of *CPT II* exons 4 and 5 were performed using AmpliTaq PCR kits (Applied Biosystems). The reaction mixture contained 2 μl buffer, 2 μl of 2 mM dNTP, 1 μl forward and reverse primers (10 pmol), 0.12 μl AmpliTaq and 1 μl genomic DNA (30 ng). Primer sequences for exons 4 and 5 were constructed based on the GenBank database in the National Center for Biotechnology Information (NCBI). For exon 4, forward and reverse primers were 5′-GGAAATCCAGGCACATCTGA-3′ and 5′–TAGCTGCTGTGATGCCTGTC-3′, respectively, and for exon 5, 5′-TCCTGAGACTCTGGTTTTCCA-3′ and 5′-TGATGGTAGCTTTTCATCTGC-3′. The PCR amplification protocol was as follows: denaturation at 95 °C for 9 min, followed by 35 cycles of denaturation at 95 °C for 30 s, annealing at 55 °C for 30 s, and extension at 72 °C for 1 min. The final extension was performed at 72 °C for 7 min. The sequences of the PCR products of *CPT II* exons 4 and 5 were analyzed with an ABI PRISM BigDye Terminator Cycle Sequencing FS Ready Reaction Kit using a sequencer (310 Genetic Analyzer; Applied Biosystems). When two heterozygous genotypes ([1055T > G/F352C] and [1102G > A/V368I]) in *CPT II* exon 4 were recognized in the patients, TA cloning was performed (Invitrogen). After purification of *CPT II* exon 4 PCR products by the QIAquick purification kit (Qiagen), they were subcloned into pCR2.1 vector (Invitrogen). The cloned *CPT II* gene was sequenced,

Table 1
Patients, clinical information and *CPT II* genotype.

Patient number	Pathogen	Sex	Age, y:m	Diagnosis	Outcome		*CPT II* genotype
					Motor	Intellectual	
1	Influenza A	Female	3:01	AESD	Mild	Moderate	6
2	NI	Female	1:01	AESD	Severe	Severe	8
3	HHV6	Female	0:09	ANE	Mild	Mild	8
4	NI	Male	1:00	ANE	Normal	NA	6
5	HHV6	Male	0:08	AESD	Moderate	Normal	6
6	HHV6	Female	1:00	AESD	Normal	Normal	6
7	HHV6	Female	0:10	AESD	NA	NA	5
8	HHV6	Female	0:11	AESD	Mild	Mild	6
9	NI	Female	0:09	ANE	NA	NA	8
10	Influenza	Female	1:05	ANE	Severe	Severe	5
11	RS virus	Male	0:11	ANE	Profound	Profound	9
12	NI	Female	0:11	AESD	NA	NA	8
13	NI	Female	1:11	AESD	NA	NA	6
14	RS virus	Female	1:09	AESD	NA	NA	6
15	HHV6	Male	1:00	AESD	Profound	Profound	9
16	HHV6	Male	0:10	AESD	Normal	Normal	7
17	NI	Female	3:04	AESD	NA	NA	9
18	Rotavirus	Male	1:03	ANE	Normal	Normal	6
19	HHV6	Female	1:11	AESD	NA	NA	8
20	Influenza B	Female	3:02	AESD	Severe	Severe	9
21	Adenovirus	Male	1:02	AESD	Normal	Normal	1
22	NI	Male	0:09	ANE	Normal	Normal	8
23	RSvirus	Female	0:07	AESD	Normal	Normal	5
24	NI	Female	1:01	ANE	NA	NA	6
25	NI	Female	3:00	AESD	NA	NA	6
26	Mycoplasma	Male	0:09	AESD	Normal	Normal	1
27	NI	Male	1:07	ANE	Normal	Normal	9
28	Influenza	Female	8:05	ANE	Normal	Normal	9
29	HHV6	Female	1:05	AESD	Normal	Normal	7

NI, not identified.
NA, not available.
CPT II genotype numbers are the same as those defined by Chen et al. [5].

and the haplotype of *CPT II* was determined. Instead of direct sequencing, real-time PCR was conducted using a Taq-Man probe in control subjects. Two genotypes in *CPT II* exon 4 were discriminated after PCR amplification using Faststart Universal Probe Master ROX (Roche). The reaction mixture contained 12.5 μl Faststart Universal Probe Master ROX, 2.2 μl of each primer, 6.4 μl distilled water, 1.2 μl of each probe, and 1 μl genomic DNA (30 ng). Sequences of the primers and real-time PCR probes were constructed based on the GenBank database in the NCBI. For real-time PCR, forward and reverse primers were 5′-ATTAAGGACCTTGTCCACT-3′ and 5′-TGAGCACTGCCACACCATCA-3′, respectively. Real-time PCR probes for F352C were 5′-FAM-ACAAACCGCTGGTTTGATAAA-3′ and 5′-VIC-ACAAACCGCTGGTGTGATAAA-3′, and those for V368I were 5′-FAM-TGGCTCTACTGCCGTCCACTTT-3′ and 5′-VIC-TGGCTCTACTGCCATCCACTTT-3′. Real-time PCR was performed under the following conditions: the first denaturation at 95 °C for 10 min, followed by 40 cycles of denaturation at 95 °C for 15 s, and annealing at 60 °C for 1 min using the ABI PRISM 7000 sequence detection system (Applied Biosystems).

3.2. Statistical methods

Differences in the demographic characteristics of the genotypes between patients and controls were assessed by χ^2-test, or when the χ^2-test was not valid, Fisher's exact test was used for categorical data. Significant differences were defined as $p < 0.05$ in conditional analysis. Odds ratios and associated 95% confidence intervals were calculated using Microsoft Office Excel 2007.

4. Results

Direct sequencing of exons 4 and 5 showed heterozygosity for [1055T > G/F352C], [1102G > A/V368I], and [1939A > G/M368I] in a subpopulation of both patients and controls. When a patient showed heterozygosity in two SNPs of exon 4, TA cloning was performed. We screened 100 controls by allelic discrimination using Taq-Man probes before direct sequencing. TA cloning was also performed in the controls classified into the heterozygous SNP group. According to the genotype definition of *CPT II* by Chen et al. [6], twenty-nine patients and one hundred controls were assorted into

six and eight genotype groups, respectively. In regard to the three polymorphic variations of *CPT II*, F352C, V368I and M647V, nine of the thrity-six expected genotypes were observed in the controls. The [1055T > G/F352C] substitution has been reported only in East Asians and not in Caucasians (rs2229291 on NCBI, http://www.sanger.ac.uk), whereas [1102G > A/V368I] and [1939A > G/M647V] substitutions have been reported in both races [9,10]. The [1939A > G/M647V] polymorphism has rarely been reported in humans. In this study, allele C in F352C was linked to both allele I in V368I and allele M in M647V in patients. Polymorphism [1939A > G/M647V] of *CPT II* was not found in patients; therefore, only six groups were recognized in the patients. The most frequent genotype was FVM–FIM (type 6) in both patients and controls. Each genotypic distribution revealed no significant difference between patients and controls. ($p = 0.176$, Table 2).

Next, we studied the allelic frequency of F352C between patients and controls, since this SNP was present only in Asian populations (rs2229291 on NCBI, http://www.sanger.ac.uk). The frequency of F352C was significantly higher in patients than in controls ($p = 0.011$, OR = 2.44, 95%CI = 1.21–4.94) (Table 3). The frequency of C allele was higher in patients (27.6%) than in controls (13.5%). All patients who had C allele in F352C had C-I-M combination. CPT II enzymatic activity with CIM haplotype is reported to be about one third of that with the FVM or FIM haplotype [6]. Therefore, we compared the frequency of having 0, 1 and 2 CIM alleles in patients and controls (Table 4). The frequency of having the CIM allele was significantly higher in patients than in controls ($p = 0.029$). To investigate whether the genotypes relate to different syndromes, we compared genotype distribution between patients with AESD and ANE, and found no difference in genotype distribution between them ($p = 0.773$) (data not shown).

Finally, we compared the allelic frequency of F352C between patients with a good and poor prognosis.

Table 4
The number of CIM haplotype in patients and controls.

CIM	Patients		Control	
	N	Frequency (%)	N	Frequency (%)
2	2	0.07	1	0.01
1	12	0.41	25	0.25
0	15	0.52	74	0.74
Total	29		100	

The frequency of having CIM haplotype was significantly different between patients and controls ($p = 0.029$).

Table 2
Genetic distribution of *CPT II*.

	Genotypes			Alleles	Patients		Controls	
	F352C	V368I	M647V		*N*	Frequency (%)	*N*	Frequency (%)
Type 1	FF	VV	MM	FVM–FVM	2	0.069	8	0.080
Type 2	FF	II	VV	FIV–FIV	0	0.000	0	0.000
Type 3	FF	VI	MV	FVM–FIV*	0	0.000	4	0.040
Type 4	FF	II	MV	FIM–FIV	0	0.000	10	0.100
Type 5	FF	II	MM	FIM–FIM	3	0.103	18	0.180
Type 6	FF	VI	MM	FVM–FIM	10	0.345	34	0.340
Type 7	CC	II	MM	CIM–CIM	2	0.069	1	0.010
Type 8	FC	II	MM	FIM–CIM	6	0.207	13	0.130
Type 9	FC	VI	MM	FVM–CIM	6	0.207	12	0.120
Total					29		100	

The nine genotypes were classified according to the diffinition by Chen et al. [6].
The difference in distribution between patients and controls was not statistically significant ($p = 0.176$).
* Haplotypes not determined.

Table 3
Allelic frequency of F352C and V368I.

Polymorphism	Allele	Patients($N = 29$)		Controls($N = 100$)		Test for allele frequency	
		N	Frequency (%)	*N*	Frequency (%)	*p* Value	Odds ratio (95%CI)
F352C	F	42	72.41	173	86.5	0.011	2.44
	C	16	27.59	27	13.5		(1.21–4.91)
V368I	V	20	34.48	66	33	0.832	1.07
	I	38	65.52	134	67		(0.58–1.98)

p value was calculated by chi-square test.
Odds ratio was shown for minor allele (C in F352C and V in V368I) versus major allele (F in F352C and I in V368I).

Table 5
Comparison of outcomes among genotypes in F352C of patients.

Genotypes	Outcome		
	Good	Poor	Total
F/F	9	1	10
F/C	4	4	8
C/C	2	0	2
Total	15	5	20

There was no statistical difference of genotype distribution between good and poor prognosis ($p = 0.154$).

Descriptions of the prognoses were available in twenty out of twenty-nine patients (Table 1). Of the ten patients who had F/F genotype, nine recovered completely or survived with mild neurological dysfunction, whereas one patient (Case 10) had severe sequelae. Of the eight patients who had the F/C genotype, four had a good prognosis, and the remaining four were left with severe neurological dysfunction. Both patients with the C/C genotype recovered completely. In regard to genotype distribution, there was no statistical difference between the good and poor prognosis ($p = 0.154$) (Table 5).

We paid attention to the clinical findings of two patients with the C/C genotype (Cases 16 and 29). In both cases, the antecedent infection was exanthema subitum. Clinical symptoms and brain MRI findings were typical of AESD. Case 16 had rhabdomyolysis, with a transient elevation of serum creatine kinase up to 30,040 U/ml, whereas Case 29 showed no particular laboratory data, except for transient thrombocytopenia.

5. Discussion

The results of the present study demonstrated that several SNPs in the *CPT II* gene are a risk factor for the onset of AESD and ANE, following various antecedent infections. The frequency of acute encephalopathy is higher in East Asians than in Caucasians [1]. It is noteworthy that the frequency of this substitution was significantly higher in our patients than in controls, since the [1055T > G/F352C] SNP in *CPT II* exon 4 has been reported only in East Asians, and not in Caucasians (rs2229291 on NCBI, http://www.sanger.ac.uk). Moreover, it has already been reported that this substitution induces an alteration of enzyme activity [11]. Chen et al. measured CPT II activity at 37 and 41 °C in COS-7 cells over-expressing *CPT II* variants, and found that the CIM haplotype shows the lowest activity in both conditions. They also reported a difference in the frequency of the FVM–CIM genotype between patients with influenza-associated encephalopathy and control subjects [6]. In the present study, we demonstrated that the frequency of the CIM haplotype, including not only FVM-CIM but also CIM–CIM and FIM–CIM, was significantly higher in patients than in controls. Considering the lowest enzyme activity of CPT II with the CIM genotype, our finding is in good agreement with the previous study [6], and extends the association to acute encephalopathy following various infectious diseases caused by HHV6, RS virus, rotavirus, adenovirus and mycoplasma. With regard to the F/F, F/C and C/C genotypes and the clinical outcome, the present study failed to show a significant correlation, possibly due to the limited number of patients.

We paid special attention to the clinical findings in the two patients with the homozygous C/C genotype, since this genotype is assumed to show the most prominent thermolability, thereby producing the most severe clinical presentation. Contrary to our expectations, the two patients recovered without any sequelae; however, the clinical features of Case 16 were noteworthy because this patient presented with transient rhabdomyolysis during the clinical course of acute encephalopathy. In this context, there is a report of a patient with CPT II deficiency due to homozygous S113L mutation, who showed recurrent rhabdomyolysis and myoglobinemia [12]. In some patients with CPT II deficiency, virus infection or long fasting triggers an episode resembling acute encephalopathy [8]. These similarities in clinical picture implicate the alteration of CPT II activity in the cerebral and muscular disorders of Case 16 with the C/C genotype.

We also compared *CPT II* genotype distribution between AESD and ANE patients, and found no significant difference. Our results show that the same polymorphism of *CPT II* is associated with both syndromes. This finding is interesting because their clinical phenotypes are quite different from each other, suggesting distinct pathomechanism. One possible explanation is that AESD and ANE share a common route of pathogenesis, which is affected by the alteration of CPT II activity at high body temperature. Another possibility is that changes of CPT II are linked to the pathogenesis via a pathway specific to each syndrome.

In conclusion, the present study extended the findings of the previous study of Chen et al. that revealed the association of a single CPT II genotype with influenza-associated encephalopathy with a poor prognosis [6]. We found that the frequency of the CIM allele was associated with the onset of acute encephalopathy with various preceding infections and variable prognosis. The thermolabile phenotype of CPT II variation predisposes infants and children to two distinct syndromes, AESD and ANE.

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References

[1] Mizuguchi M, Yannanouchi H, Ichiyama T, Shiomi M. Acute encephalopathy associated with influenza and other viral infections. Acta Neurol Scand 2007;115(Suppl. 4):45–56.

[2] Takanashi J, Oba H, Barkovich AJ, Tada H, Tanabe Y, Yamanouchi H, et al. Diffusion MRI abnormalities after prolonged febrile seizures with encephalopathy. Neurology 2006;66:1304–9.

[3] Mizuguchi M. Acute necrotizing encephalopathy of childhood: a novel form of acute encephalopathy prevalent in Japan and Taiwan. Brain Dev 1997;19:81–92.

[4] Sugaya N. Influenza-associated encephalopathy in Japan: Pathogenesis and treatment. Pediatr Int 2000;42:215–8.

[5] Jones CM, Dunn HG, Thomas EE, Cone RW, Weber JM. Acute Encephalopathy and Status Epilepticus Associated with Human Herpes Virus 6 Infection. Develop Med Child Neurol 1994;36:646–50.

[6] Chen Y, Mizuguchi H, Yao D, Ide M, Kuroda Y, Shigematsu Y, et al. Thermolabile phenotype of carnitine palmitoyltransferase II variations as a predisposing factor for influenza-associated encephalopathy. FEBS Lett 2005;579:2040–4.

[7] Woeltje KF, Esser V, Weis BC, Cox WF, Schroeder JG, Liao ST, et al. Inter-tissue and Inter-species Characteristics of Mitochondrial Carnitine Palmitoyltransferase Enzyme System. Biol Chem 1990;265:10714–9.

[8] Tamaoki Y, Kimura M, Hasegawa Y, Iga M, Inoue M, Yamaguchi S. A survey of Japanese patients with mitochondrial fatty acid beta-oxidation and related disorders as detected from 1985 to 2000. Brain Dev 2002;24:675–80.

[9] Shiomi M, Ishikawa J, Togawa M, Okazaki S, Kuki I, Kimura S, et al. A concept of acute encephalopathy with febrile convulsive status epilepticus (AEFCSE) and theophylline as one of its precipitating causes (in Japanese). No To Hattatsu 2008;40:122–7.

[10] Wataya K, Akanuma J, Cavadini P, Aoki Y, Kure S, Invernizzi F, et al. Two CPT2 mutations in three Japanese patients with carnitine palmitoyltransferase II deficiency: Functional analysis and association with polymorphic haplotypes and two clinical phenotypes. Hum Mutat 1998;11:377–86.

[11] Olpin SE, Afifi A, Clark S, Manning NJ, Bonham JR, Dalton A, et al. Mutation and biochemical analysis in carnitine palmitoyltransferase type II (CPT II) deficiency. J Inherit Metab Dis 2003;26:543–57.

[12] Handig I, Dams E, Taroni F, Vanlaere S, deBarsy T, Willems PJ. Inheritance of the S113L mutation within an inbred family with carnitine palmitoyltransferase enzyme deficiency. Hum Genet 1996;97:291–3.

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Short communication

Kawasaki disease complicated by mild encephalopathy with a reversible splenial lesion (MERS)

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ABSTRACT

We reported four patients (2 to 10 years) with Kawasaki disease complicated by clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS). All were treated with γ-globulin (2 to 6 g/kg) after the diagnosis of Kawasaki disease, the fever being alleviated between day 6 and 25. One of two patients exhibiting a poor response to γ-globulin had a cardiac aneurysm as a sequela. Their neurological manifestations (delirious behavior and drowsiness), laboratorial hyponatremia, and radiological abnormalities completely disappeared. It is important for pediatricians to acknowledge that MERS can be observed in patients with Kawasaki disease, especially in older children, and that they might be at high risk for cardiac abnormalities.

1. Introduction

Kawasaki disease (KD) is an acute febrile, systemic vasculitis of unknown pathogenesis, most often affecting young children under 5 years old. The most important complication of KD is coronary arterial aneurysms (in 15-25% of untreated children), which may cause ischemic heart disease and sudden death [1,2]. Irritability, lethargy, transient unilateral facial nerve palsy are sometimes observed, and pleocytosis in the cerebrospinal fluid (CSF) is found in around 40% [1–4], however, febrile convulsions and acute encephalopathy are extremely rare [5–7].

Magnetic resonance imaging (MRI) finding of a reversible lesion with transiently reduced diffusion in the splenium of the corpus callosum has been reported in patients with clinically mild encephalitis/encephalopathy, leading to a new clinical-radiological syndrome, clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) [8,9]. We present here four patients with KD complicated by MERS, which suggest that MERS is a more common neurological complication than previously considered.

2. Methods

Information on patients with KD who developed MERS was collected retrospectively after approval by the institutional review board of the Kameda Medical Center. The diagnosis of KD and MERS were established according to diagnostic criteria [1,2,8], respectively. We reviewed the clinical charts of the patients in order to accrue information on symptoms, medication, treatment, outcome, and results of CSF analysis, MRI, and electroencephalography (EEG).

3. Results

Four previously healthy Japanese patients (1 male and 3 females, aged from 2 to 10 years) met the criteria for enrollment in this study, with the onset from March 2010 to February 2011. The clinical and radiological records of the four patients are summarized in Table 1. All were treated with γ-globulin (2 to 6 g/kg) after the diagnosis of KD, the fever being alleviated between day 6 and 25. Two patients exhibiting a poor response to γ-globulin were additionally treated with cyclosporine and infliximab (patient 1), and prednisolone

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Table 1
Data for Kawasaki disease with MERS.

Pt.	Age/Sex	Tx for KD γ-globulin	Other therapies	End of fever	Na level (lowest) follow up	Coronary sequelae	Consciousness disturbance	Duration delirium
1	8/M	2 g/kg × 3 (D5, D7, D9)	cyclosporine infliximab	D21	119 (D6) 137 (D40)	AN (5 mm)	Mild drowsiness D1-8	D1-8
2	7/F	2 g/kg (D5)		D6	129 (D3) 139 (D9)	No	Drowsiness D3-5	D3-5
3	10/F	2 g/kg × 2 (D3, D5)		D6	127 (D4) 138 (D13)	No	Drowsiness D3-5	D3-5
4	2/F	2 g/kg × 2 (D9, D20)	prednisolone	D25	134 (D9) 139 (D45)	No	Drowsiness D10-14	D10-12
	14/F	1.8 g/kg (D5)		D13	128 (D6) 142 (D25)	AN (8 mm)	Mild drowsiness D5-7	D5-7
	7/F	2 g/kg (D4)		D5	131 (D3) 141	No	Drowsiness D2-3	D2-3

ABBREVIATIONS
Pt, patient; Tx, therapy; M, male; F, female; D, day; AN, aneurysm; CC, cell count; WM, white matter; CR, complete recovery.

Delirious behavior Components	Seizure	CSF study	MRI results	EEG results	Neurological outcome	
Incoherent speech, unresponsiveness	No	Normal (D6)	Splenium (D7) Normal (D15)	Frontal slow (D6) Normal (D14)	CR	
Impulsive behavior, visual hallucinations, incoherent speech	No	Normal (D3)	Splenium (D4) Normal (D10)	Diffuse slow (D4) Normal (D9)	CR	
Emotional changes (laughter, weeping, fear), visual hallucinations, incoherent speech	No	Normal (D3)	Splenium + WM (D3) Normal (D7)	Diffuse slow (D3) Normal (D6)	CR	
Visual hallucinations, misperceptions	No	Normal (D10)	Splenium (D10) Normal (D17)	Normal (D10)	CR	
Visual hallucinations	No	CC 16/mm^3 (D7)	Splenium (D10) Normal (D14)	Normal (D11)	CR	[10]
Impulsive behavior, visual hallucinations, incoherent speech	No	Normal (D3)	Sp (D3) Normal (D11)	Diffuse slow (D3)	CR	[11]

(patient 4). One patient (patient 1) had a cardiac aneurysm (5 mm) as a sequela.

All four patients presented with fluctuating delirium with onset between day 1 and 10, and a duration of 3 to 8 days, and all showed mild to moderate drowsiness between the episodes of delirious behavior. The results of neurological examinations were unremarkable except for the delirium and drowsiness. CSF analysis was normal in all patients. The Na level during neurological symptoms decreased to 119–134 mEq/l, which had become normal at the time of follow-up. MRI performed during their neurological manifestations (day 3 to 10) revealed homogenously reduced diffusion in the splenium (patients 1, 2, and 4) (Fig. 1-A) or the splenium and symmetrical subcortical white matter (patient 3), which had completely disappeared by the time of follow-up (day 7 to 17) with an interval of 4 to 8 days (Fig. 1-B). No specific treatment for MERS was performed for any patient; however, their neurological manifestations disappeared completely. EEG showed slow waves in three patients (became normal on follow-up EEG), and normal in another.

4. Discussion

Encephalitis or encephalopathy is an extremely rare complication of KD. Actually, none of 540 patients with KD presented with encephalitis/encephalopathy [4]. As far as we know, there have been only six patients with KD complicated by MERS (Table 1) [10,11], including the present four patients, their onset ranging from March 2010 to February 2011. The number of KD patients in 2010 in Japan has been reported to be 12,755, and that over 6 years being 466 [12]. The incidence of MERS in KD over 6 years, therefore, seems to be at least 1% (5/466).

All six patients (mean age, 8.0 years) presented with delirious behavior and drowsiness with hyponatremia (119–134 mEq/l); and a homogenously reduced diffusion in the splenium, all of which completely recovered or disappeared. These clinical, laboratorial, and radiological findings are typical of MERS (mean age, 9.0 years; serum sodium level, 131.8 ± 4.1 mEql/l) [8,13]. MERS has been reported to be an encephalitis or encephalopathy associated with infection, such as influenza or rotavirus [8,9]. It is important for pediatricians to acknowledge that MERS can be observed in patients with KD, which is an acute febrile systemic vasculitis, not directly related to a pathogen.

What is the possible mechanism underlying MERS with KD? The exact pathogenesis of MERS is uncertain, however, MERS seems to comprise cerebral edema due to electrolyte/water imbalance, including hyponatremia, as an underlying pathophysiology [8,13]. Activation of the immune system seems to be a central feature of KD, and the concentrations of many proinflammatory cytokines and chemokines, including tumour necrosis factor α, interleukins 1, 6, and 8, and vascular endothelial growth factor (VEGF), are elevated during the acute phase [1,2]. Elevated VEGF could result in vascular leakage, hypoalbuminemia, and noncardiac edema [14]. Actually, cerebral edema has been histopathologically observed in patients with KD [15], which could possibly progress to MERS.

Two of the six patients with KD complicated by MERS (Table 1, patient 1 and one patient previously reported [10]) had a cardiac aneurysm as a sequela. The duration of a fever has been confirmed to be a predictor of a coronary artery aneurysm in KD [1]. Other independent risk factors have been reported, including an elderly onset and the presence of hyponatremia. Children 6 years and older account only for around 5% of patients with KD [16], however, they often have delays in diagnosis, and an increased incidence of cardiovascular abnormalities (20% vs. 15% under 6 years) [16,17]. The hyponatremia observed in 45% in patients with KD has also been reported to be an independent risk factor for cardiovascular sequelae [18]. Actually, the two patients having a cardiac aneurysm fulfilled the triple risks, prolonged fever (21 and 13 days), elderly onset (8 and 14 years), and hyponatremia (119 and 128 mEq/l). Elderly onset and hyponatremia are also characteristic of MERS, therefore, it is reasonable that patients with KD complicated by MERS likely have risk factors for cardiac abnormalities.

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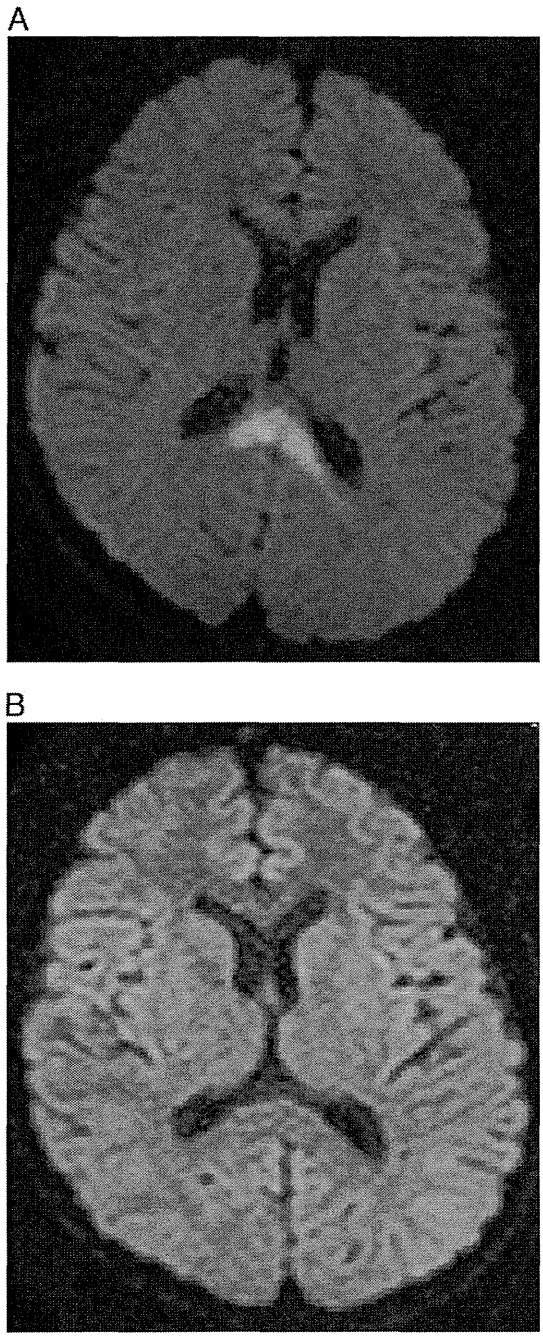

Fig. 1. Diffusion-weighted image of patient 1 on day 7 (A) shows a high signal lesion in the splenium of the corpus callosum, which disappears on day 15 (B).

It seems that cardiac abnormalities are more common in patients with KD having neurological manifestations, for example, two of the six patients with MERS, 2/2 and 2/5 with transient hemiplegia and facial nerve palsy, respectively [4,7]. Those with transient consciousness disturbance during the acute phase of KD have also been reported to have coronary aneurysms in 19% (6/32) [7]. It is possible that the severity of KD (severe vasculitis) may result in neurological manifestations. Further clinical, radiological and immunological studies are necessary to clarify the frequency, mechanism, and prognosis of KD complicated by MERS.

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References

[1] Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tana LY, Burns JC, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the committee on rheumatic fever, endocarditis, and Kawasaki disease, council on cardiovascular disease in the young, American Heart Association. Pediatrics 2004;114:1708–33.
[2] Burns JC, Glodé MP. Kawasaki disease. Lancet 2004;364:533–44.
[3] Dengler LD, Capparelli EV, Bastian JF, Bradley DJ, Glode MP, Santa S, et al. Cerebrospinal fluid profile in patients with Kawasaki disease. Pediatr Infect Dis J 1998;17:478–81.
[4] Terasawa K, Ichinose E, Matsuishi T, Kato H. Neurological complications in Kawasaki disease. Brain Dev 1983;5:371–4.
[5] Yoshikawa H, Abe T. Febrile convulsion during the acute phase of Kawasaki disease. Pediatr Int 2004;46:31–2.
[6] Tabarki B, Mahdhaoui A, Selmi H, Yacoub M, Essoussi AS. Kawasaki disease with predominant central nervous system involvement. Pediatr Neurol 2001;25:239–41.
[7] Imai K, Kawabe Y, Awaya A, Asaka A. A case of Kawasaki disease accompanied by encephalopathy during acute phase (in Japanese). Jpn Soc Emerg Pediatr 2009;8:50–5.
[8] Takanashi J. Two newly proposed encephalitis/encephalopathy syndromes. Brain Dev 2009;31:521–8.
[9] Tada H, Takanashi J, Barkovich AJ, Oba H, Maeda M, Tsukahara H, et al. Clinically mild encephalitis/encephalopathy with a reversible splenial lesion. Neurology 2004;63:1854–8.
[10] Itamura S, Kamada M, Nakagawa N. Kawasaki disease complicated with reversible splenial lesion and acute myocarditis. Pediatr Cardiol 2011;32:696–9.
[11] Sato T, Ushiroda Y, Oyama T, Nakatomi A, Motomura H, Moriuchi H. Kawasaki disease-associated with MERS: pathological insights from SPECT findings. Brain Dev 2011, doi:10.1016/j.braindev.2011.09.015.
[12] Japan Kawasaki Disease Research Center. The 21th nationwide survey of Kawasaki disease in 2009–2010 (in Japanese). www.jichi.ac.jp/dph/kawasakibyou/20110915/mcls21report.pdf.
[13] Takanashi J, Tada H, Maeda M, Suzuki M, Terada H, Barkovich AJ. Encephalopathy with a reversible splenial lesion is associated with hyponatremia. Brain Dev 2009;31:217–20.
[14] Terai M, Honda T, Yasukawa K, Higashi K, Hamada H, Kohno Y. Prognostic impact of vascular leakage in acute Kawasaki disease. Circulation 2003;108:325–30.
[15] Amano S, Hazama F. Neural involvement in Kawasaki disease. Acta Pathol Jpn 1980;30:365–73.
[16] Muta H, Ishii M, Sakaue T, Egami K, Furui J, Sugahara Y, et al. Older age is a risk factor for the development of cardiovascular sequelae in Kawasaki disease. Pediatrics 2004;114:751–4.
[17] Stockheim JA, Innocentini N, Shulman ST. Kawasaki disease in older children and adolescents. J Pediatr 2000;137:250–2.
[18] Watanabe T, Abe Y, Sato S, Uehara Y, Ikeno K, Abe T. Hyponatermia in Kawasaki disease. Pediatr Nephrol 2006;21:778–81.

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