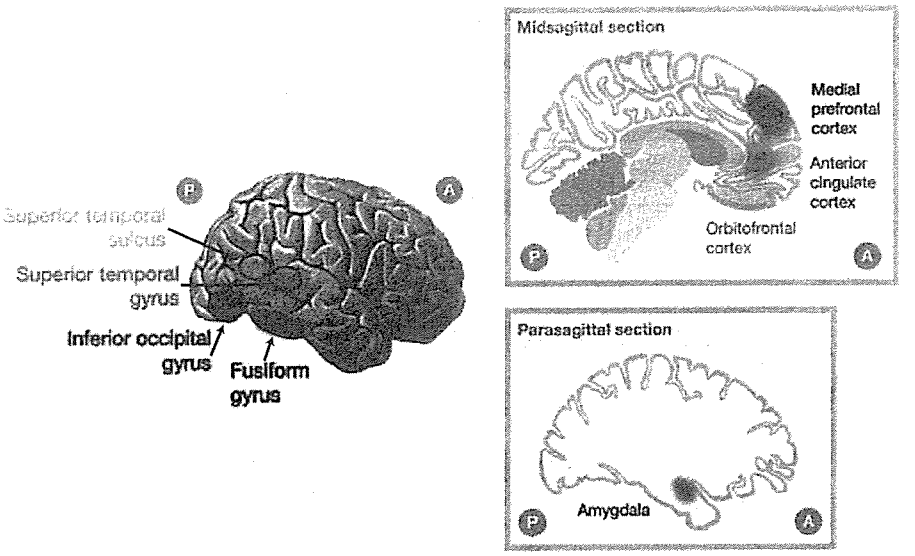

図3　Social Brain（Baron-Cohen ら，2005）

表6　高機能自閉症の併存障害

・学習障害	・適応障害
・ＡＤ／ＨＤ	・不安障害
・反抗挑戦性障害	・チック，トウレット障害
・行為障害	
・気分障害	

表7　自閉症の薬物療法

・特殊な治療
　SSRI，リチウム：自閉性気分障害
　プリン制限食，セクレチン
・個々の症状に対する治療
　メチルフェニデート，クロニジン：多動性
　メラトニン，抗ヒスタミン剤：睡眠障害
　クロニジン，リスペリドン：攻撃性
・非特異的治療
　非定型抗精神病薬，SSRI，Vit B6，免疫療法
　少量ドパミン

なかったことによるものが多く，特に，保育所や幼稚園での集団行動を確認することが大切である．Gillberge は[21]このような症例をDAMP症候群としているが，今後，両者の関係の神経学的な基盤を研究することが求められる．反抗挑戦性障害や行為障害の併存は注意して対応する必要がある．わが国では研究の途に付いたところであるが，欧米では触法行為者のなかに発達障害の頻度が高いことが報告されている[22]．特に，発達障害に虐待が生じやすいが，幼少児期に被虐待的養育体験が高い発達障害児は体質など様々な要因も加味し反社会性の行動が生じやすいともいわれている[23]．摂食障害，不登校，引きこもりなどの適応障害も合併しやすく，これらの背景原因として高機能自閉症があることも多い．トウレット障害も合併しやすいが，高機能自閉症で状況が悪くなるとチック症を発症することがよく見られ，彼らの生活がうまく行ってるか否かの指標にもなる．

8．介入

早期発見と早期介入がが大切であり，自閉症の予後に関係する要因として①5歳以前に言葉が出現すること，②知的レベルが高いこと，③言葉の理解の良いこと，④早期介入がある[24][25]．介入には治療教育と医学的治療がある．治療教育の方法として行動分析技法を用いた行動療法，社会生活技能訓練，ソーシャルストーリー，コミック会話，保護者に行動療法を指導し過程で実行してもらうペアレントトレーニングなどがある．医学的薬物治療には出現する行動上の問題に対して行われることが中心であり（表7），大量ビタミンB6，セクレチン，テトラヒドロビオプテリン，5HTPなど，原因仮説に基づいた自閉症そのものへの治療は効果がはっきりしない[26]．

B　特別支援教育

1．特別支援教育の定義

平成15年3月の「今後の特別支援教育のあり方について（最終報告）」[2]によると「特別支援教育とは，従来の特殊教育の対象だけでなく，LD，AD/HD，高機能自閉症も含めて障害のあり児童生徒の自立や社会参加に向けて，その一人一人の教育的ニーズを把握して，そのもてる力を高め，生活や学習上の困難を改善又は克服するために，適切な教育や指導を通じて必要な支援を行うものである．」となっている．

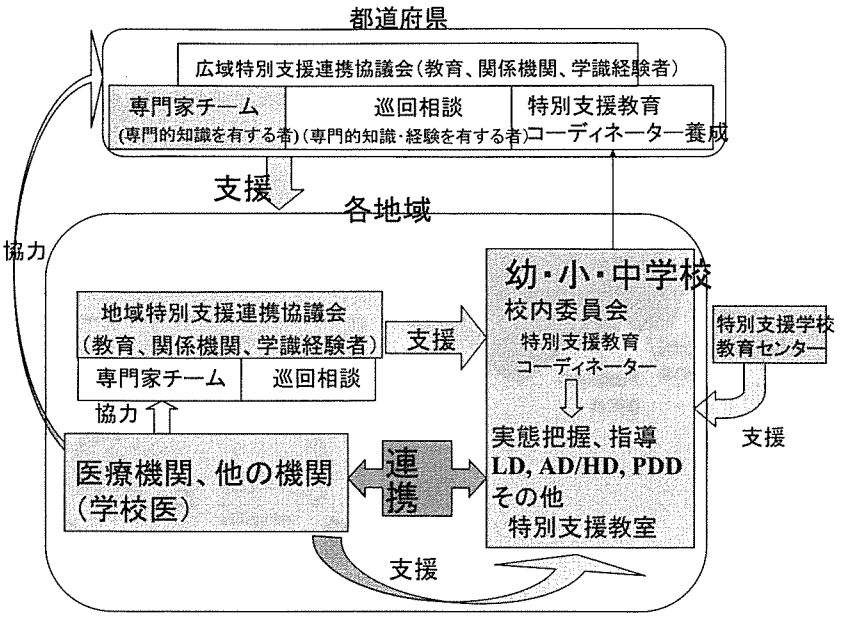

図4　特別支援教育体制

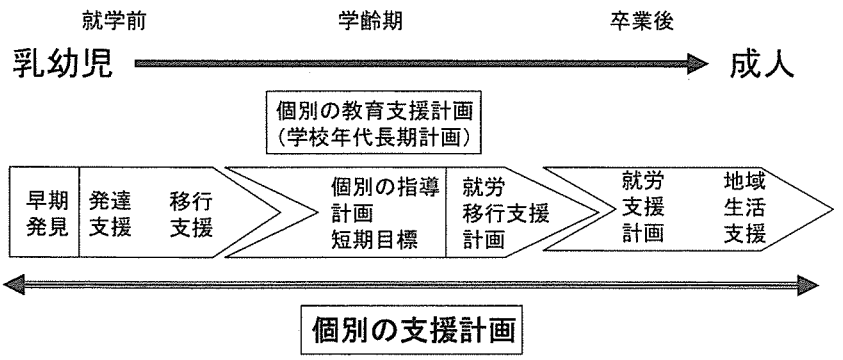

図5　個別の教育支援計画

2. 特別支援教育の現状について

平成12年から始まった学習障害(LD)に対する指導体制の充実事業を引き継ぎ，平成15年度からLDに加えAD/HD，高機能自閉症を含めた支援体制を構築するために「特別支援教育推進体制事業」が全国的に行われてきた．各地方では実態把握に始まり，AD/HDや高機能自閉症のある児童生徒の指導体制の整備，小・中学校に設置された校内委員会で中心的・指導的役割を担う特別支援教育コーディネーターの養成・指定，巡回相談事業が行われてきた．質の高い教育支援を支えるためのネットワークである調査研究運営会議(後に広域特別支援連携協議会)を設置し，その下に専門的意見を述べる専門家チーム，学校に指導・助言を行う巡回相談員を置き小・中学校を支える形となっている．従来の盲・聾・養護学校は特別支援学校としてセンター的機能を果たし，教育センターと共に，小・中学校を支援する．小・中学校では校内委員会を設け特別支援教育コーディネーターが中心となり担任と共に保護者，関係諸機関と連携・調整しながら障害のある児童生徒の実態把握を行い，一人一人の教育的ニーズを把握して個別の教育支援計画，個別の指導計画を立て指導する．個別の教育支援計画は新「障害者基本計画」における個別の支援計画の学校版であり，長期の見通しを持って立てられるものであり，実行しその結果を評価し，その結果子どもの状況によっては計画の変更もありうる（図4, 5）[2)27)28)]．

この特別支援教育は学校教育法の一部を改正する法律が本年6月に通過したことから，平成19年4月1日から施行されることとなった．この法律では盲・聾・養護学校が特別支援学校となり，在籍児童生徒の教育に加え，小中学校等に在籍する障害のある児童生徒の教育について助言援助に努めること，小中学校等ではLD, AD/HD，高機能自閉症等を含む障害のある児童生徒に適切な教育を行うこととなっている．

3. 小児科医の果たす役割

われわれ小児科医は子どもの心身の健康維持，増進

を図る役割を担っており，様々な発達障害の治療，ケアを含めて診療に最初に関わる可能性が高い立場にある．軽度発達障害が疑われる子どもは軽度の知的障害，境界知能をも含めると10%を越えると思われるが，このような子どもの状況について医学的な判断を求められることも少なからずあると考えられる．このような子どもを持った保護者は，なんとなく漠然とした不安を抱いているが反面否定したいという気持ちも強い．また，場により症状の出方に変化があることから，診察室のような限られた空間や家庭では症状が見られないことも多い（集団の場でどのような行動が出るかをチェックすることが大切である）．安易に問題なしとすることは診断を遅らせ，児への対応を誤らせる恐れがある．少しでも疑いがある場合には専門の医師に紹介し判断を求めるべきと考える．日本小児神経学会ではこのような発達障害を専門に診療している全国の発達障害診療医師のリストをホームページに掲載している（http://www.yo.rim.or.jp/~JSCN/）．利用していただければ幸いである．

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特集　てんかん診療ABC

学校生活上の留意点，とくに学習・行動面の問題

橋本俊顕　鳴門教育大学障害児教育講座

要旨

近年，注意欠陥多動性障害や広汎性発達障害，学習障害が教育の場で注目を集め，その対応がなされるようになりつつある．これらの障害では脳の器質的または機能的異常があり，てんかんとの合併が多いことから，その関連性について述べる．さらに，小児のてんかんにおいて学校を含めた集団活動上の問題点についても触れる．

Key Words
ADHD
学習障害
自閉症
てんかん
予防接種

てんかんと発達障害

1. 自閉症スペクトラム

自閉症スペクトラムは対人関係の質的障害，コミュニケーションの質的障害，想像力の障害に起因するこだわり行動の三主徴とする症候群であり，脳の器質的あるいは機能的障害が背景にあると考えられている．頻度は約1～2%であり，圧倒的に男児に多い．

てんかんの合併について，Kannerの報告した11例中2例に追跡調査でてんかん発作があることが報告されており，一般人口のてんかんの有病率0.5～1.0%に比較すると高率である．Kobayashiらは[1]，就学前から成人期まで縦断的に観察し，188例（男児157例，女児31例）中36例（男児30例，女児6例）にてんかんを合併したと報告している．てんかんの発症率に男女差はみられなかった．てんかんの発症年齢は平均13.3歳であり，11～18歳にピークを認め，発作型は全身性発作が大部分であった．Danielssonらは[2]，小児期に診断された自閉症児108例を前方視的に追跡調査し，38%にてんかんの発症があり，非てんかん群に比してんかん発症群で適応行動レベルが低く，認知機能も低下していた．その1/3は2歳以前に発症しており，16%が寛解した．発作型では部分発作が多かったと報告している．自閉症におけるてん

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表1　自閉症におけるてんかん，脳波異常の頻度

著　者	年齢（歳）	症例数	てんかんの頻度	脳波異常の頻度
Chez, 2006	5.7	889	—	60.7％
Canitano, 2005	7.8 ± 2.7	46	13％	22％
Gabis, 2005	child	56	40％	—
Kagan-Kushnir, 2005	—	MEDLINE, EMBASE	20 ～ 30％	10.3 ～ 72.4％
Huges, 2005	child	59	46％	75％
Hashimoto, 2001	6.3 ± 3.5	86	21％	43％
Kawasaki, 1997	15 ～ 28	158	39.2％	60.8％
Tuchman, 1991	1 ～ 23	302	—	22.7％
Volkmar, 1990	2 ～ 33	192	21.4％	40％

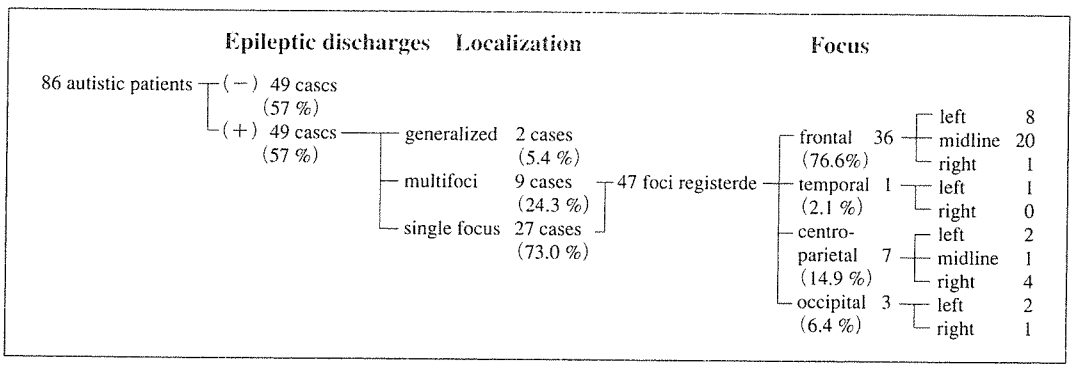

図　自閉症における脳波異常の頻度と発作波の焦点

かん発症および脳波異常の頻度について表に示す（表1）．

一方，てんかん患者の中に自閉症スペクトラムがどの程度存在するかについて，Clarke らは[3]，第三次ケアのてんかんクリニックで自閉症スクリーニング質問票による調査を行い，98例中32％が自閉症スペクトラムに該当したと報告した．発作は2歳以前に発症していることが多いとしている．

自閉症の脳波異常についても多くの報告が見られ，その頻度は10数％から70％ぐらいまで非常に幅が広い．川崎は[4]，幼少期から継時的に脳波を検査し，最終脳波検査年齢が15歳を超えていた158例（男子119例，女子39例）と同じような条件で検査された，自閉症のない知的障害児75例とを比較検討した．延べ脳波記録回数は自閉症群693回，知的障害群336回であった．発作性脳波異常の局在をF群：Fp，F，Fz，Cz，CP群：P3，4，C3，4，O群：O1，2，T群：F7，8，T3，4，5，6，D群：両側または片側全般性の5群に分けた．発作波の局在は9歳未満ではF群は40％であったが，加齢とともに増加し15歳を超えた年齢では70数％になったが知的障害群では，年齢変化がみられなかった．この発作波を脳磁図で局在を調べたところ，前頭部内側，帯状回前部に存在した．てんかんの発症は67例，39.2％で，発作型は全般発作65.7％，部分発作31.3％であった．別の調査による高機能群のてんかん発症は55例中6例，10.9％であった．てんかん発症のピークは高機能群と低機能群であまり差がなく思春期であった．

筆者らも自閉症児の睡眠時の脳波異常について検討したところ，43％に以上がみられ，その

表2　てんかん児におけるADHDの頻度

著　者	対　象	てんかん症例数	ADHDの頻度	
			多動性・衝動性または混合型	不注意型
Dunn, 2003	child	175	14％	24％
Hoare, 1991	child	108	48％	—
Bravidor, 1990	child	43	47％	—
Holdsworth, 1974	child	85	21％	42％
Dunn, 2005	review	—	30～40％	
Tan, 2005	review	—	20％＜	

約半数にてんかんが発症した．脳波異常は多焦点性であり，とくに前頭正中部に多く（図），脳波異常を合併した例では発達指数，知能指数が低値であった[5]．

Chezらは[6]，889例の自閉症スペクトラム児の24時間デジタル脳波について検討し，540例，60.7％に発作波を認めた．発作波はすべて睡眠中に出現しており，退行を示したものとそうでないものの差はなかった．発作波の焦点は右側頭葉にもっとも多かったとしている．176例にバルプロ酸が投与され正常化が82例，改善が30例にみられている．

発作波の局在については報告により異なり，中心部，中心側頭部に多い，特別な局在はないなど結果はまちまちである．今後さらに検討がなされることが必要である．

2．注意欠陥多動性障害（ADHD）

注意欠陥多動性障害は，注意力の障害，多動性・衝動性を主徴とする行動の異常を呈する症候群であり，7歳までに発症する．頻度は3～6％であり，男児に多く，一卵性双生児による研究から遺伝要因が考えられ，遺伝子の検索もなされている．前頭前野，視床，線状体の回路の障害があり，前頭葉の抑制機構の未熟性，機能異常が生じた結果であると考えられている．神経化学的には，ドパミン系およびノルアドレナリン系の異常があり，メチルフェニデートやアトモキセチンにより改善されると症状もよくなる．

ADHDの併存症として軽度精神遅滞，学習障害，広汎性発達障害，てんかん，反抗挑戦性障害，行為障害，チック障害，気分障害，不安障害などがある．

てんかん児においては，一般人口に比べてADHDの頻度は高く，約14％と2～4倍くらいである（**表2**）．行動上の問題として，多動性・衝動性を示す児の頻度は小児てんかんの28.1～39％，注意の問題を示すものは42.4％であった．1988年の米国のNational Health Interview Surveyによる調査では，5～17歳のてんかん児の中で，多動性の症状がみられたものは対象と比べ5.7倍あり，衝動性の異常行動は3.8倍であった．このようにてんかん児においては不注意，多動性・衝動性などの行動異常を呈する児の頻度が高率である．また，ADHDの児においては誘因のはっきりしない発作の頻度が2.5倍高く，とくに不注意型，混合型で高かった．このようなパターンは部分起始発作，全般性発作，特発性・潜因性発作にみられたとしており，てんかん児においてADHD，とくに不注意型はてんかんや誘因のはっきりしない発作の危険因子と考えられるとしている[7]．

不注意型の子どもは時々ボーッとして注意がそれることから，複雑部分発作や欠神発作と似た状態となり，これらとの鑑別が必要になってくる．多くの場合，不注意の行動では，子ども

は肩などにタッチされたとき，すぐに反応することができるが，短い欠神発作と区別が困難なこともある．複雑部分発作では発作後の意識朦朧状態の存在から白昼夢状態を区別しうる．しかし，ADHDでは不眠状態にあることも多く，結果として睡眠状態に陥っていることもあるので，最終的にはビデオ脳波モニターによる発作時脳波の確認が必要となる．

さらに，不注意に関して，てんかん発作波の影響も考えられる．従来，臨床的なてんかん発作症状のない脳波上にみられる発作波だけでは，薬物治療の対象にしないことが多かったが，てんかん発作波の出現時に軽度の注意状態の欠損がみられることが明らかになってきた．Aartsら[8]は，サブクリニカルな発作波の発射中に一過性の認知の途絶え（transient cognitive impairment）があることを報告している．このような状態は発作波発射の高頻度の患者では約50％にみられ，とくに3 Hz棘徐波結合でもっともよくみられ，不規則棘徐波結合や，発作性のデルタ波群発では影響は少ないといわれている．注意や想起のテストでは，発作波の部分の約1/3に，患者の2/3に一過性の認知の途絶えがみられ，この変化は全般性発作波の量の変化に対応する．また，焦点性発作波の場合には出現部位の神経心理学的脳機能に対応した変化がみられる．

しかし一方では，ADHDで高頻度に中心・側頭部に発作波を呈する率が高く，中心・側頭部に発作波を呈したこれらの症例での認知機能に差はなかったが多動性・衝動性が目立ったとの報告も見られる[9]．

3. 学習障害

学習障害はDSM-Ⅳ-TRでは，①読字障害，②算数障害，③書字表出障害，④特定不能の学習障害，に分類されている．

読字障害での研究では，画像検査において微細な脳形成異常が見られるなどの報告が増加しており，脳になんらかの器質的もしくは機能的異常があって生じると考えられている．このようなことから，てんかんに学習上の問題が生じやすいことも事実である．Changら[10]は，2個以上のperiventricular nodular heterotopia（PNH）と，てんかんをもった10例についてMRIと神経心理学的に検討し，10例中8例に正常知能にかかわらず，読みの障害がみられたとしている．障害の程度が強かった例では，より広くPNHが分布しており，てんかんの重症度や薬剤使用とは関係がなかった．

てんかん児の中に学習障害をおこす児がどの程度存在するかについて，小児期発症の成人てんかん患者について検討したところ，約37％に学習障害がみられ，そのうち正常知能（IQ＞85）の中では57％，境界知能では67％にみられた．症候性の病因が学習障害の予知因子であり，学習障害の存在は医学的，社会的および学習の予後に影響していた[11]．

Vinayanら[12]は，中心・側頭部に棘波をもつ良性小児てんかん（BECCT）50例について検討し，教育上の問題が27例，54％にみられ，そのうち19例に学習障害をうかがわせる神経心理学的な異常があり，教育上の問題と神経心理学的な異常との間には明らかな関係があったとしている．棘波の双極子について検討し，典型的な前頭部陽性，中心・側頭部陰性で前頭・中心部にまたがる接線方向の双極子をもったものでは教育上の問題が少なく，そうでないものでは非典型的な発作が多く，教育上の問題も多かった．

発達性計算障害は未熟児，低出生体重児におこりやすく，ADHD，てんかん，発達性の言語障害などとの合併もみられ，左側頭頭頂葉領域の機能がとくに重要であるが，正常の数学的スキルに必要な両半球の神経ネットワークの機能も関係する．このようにてんかん焦点の局在と学習障害との関連について，側頭葉てんかんでは，和田テストで左半球優位であったもので読

表 3

ガイドラインA案（普通学級用）（文献14）より引用）

てんかん患児管理指導表

所見名（診断名）　　平成　　年　　月　　日

学校名　　医療機関

氏　名　　医師　　㊞

管理区分決定のめやす（発作の頻度・強度からの分類）	発作強度	
	弱	強
発作頻度	短時間の意識消失，程度の軽いけいれん発作など	外傷の危険が大きい，転倒を伴う，けいれん後も意識消失が長びく発作など
1回/日程度以上	B	A
1回/週程度以上	C	B
1回/月程度以上	C	B
1～2回/年程度	C	C
1年以上発作なし	D	C
3年以上発作なし	E	E

学校生活の区分	教室内学習	体育実技（除く水泳）	水泳	部活動
A	要注意	1対1などの厳重注意		
B	注意して可	要注意（監視が必要）		
C	可	注意して可	要注意	注意して可
D	可		注意して可	可
E	可			

学校行事，その他の活動

Ⅰ．児童生徒活動：Aは厳重注意，Bは要注意，C・Dは可
Ⅱ．食事当番・清掃：Aは厳重注意，Bは要注意，C・Dは可
Ⅲ．朝会やその他の集会：Aは厳重注意，Bは要注意，C・Dは可
Ⅳ．運動会，体育祭，球技大会：Aは厳重注意，Bは要注意，C・Dは可
Ⅴ．水泳大会，臨海学校：Aは厳重注意，B・Cは要注意，Dは必要により何らかの対策をとる必要がある
Ⅵ．遠足，見学，移動教室：Aは厳重注意，Bは要注意，C・Dは可
Ⅶ．林間学校，修学旅行：Aは厳重注意，Bは要注意，C・Dは服薬が医師の指示通り行われることが必要

区分Cは「可」であっても，場合により監視が必要．区分Dの水泳は，必要により何らか対策をとる必要がある

ガイドラインB案（特殊学級，養護学校用）（文献14）より引用）

頻度別・強度区分	教室内学習	体育実技（除く水泳）	水泳	部活動	児童活動	給食清掃当番	朝会・集会	球技大会	移動教室	林間学校行	林間学校
A	1対1などの厳重注意が必要										
B	監視下であれば可（厳重に監視）										
C	監視下であれば可（注意して監視）										
D	可		可*	可							可*
E	可										

*：必要により何らかの対策をとる必要がある

み理解，書き，計算の能力障害のあるものの，頻度は左側頭葉に焦点のあるもので高率で75％以上であった．逆に右焦点では10％未満であった．すなわち，優位半球でのてんかんの発症は，学習障害の頻度が高くなることが予見される[13]．

てんかん児の保育所・幼稚園・学校生活について

1．スポーツ，課外活動，その他

てんかん児の学校でのスポーツや課外活動については原則参加の方向であるが，保護者が学校に病名を伝えているかどうかが問題になってくる．伝えていない場合には，この原則は当てはまらない．学校への病名告知は理想であるが，現実にはさまざまな問題があり躊躇せざるをえないこともある．しかし，発作頻度が比較的高いときには告知せざるをえないと思われる．学校行事への参加に関して，厚生労働省心身障害研究「小児慢性疾患のトータルケアに関する研究」（1992）によるガイドラインが参考になる[14]（表3）．

Wongらは[15]，てんかん児の生活活動について調査してんかんでない同胞と比較した．てんかん児では同胞より活動性が少なく，肥満気味であった．とくに，3剤以上の抗てんかん薬を服用している児ではスポーツに関与することが少なく，発作頻度が関係することがうかがわれたが，スポーツにかかわることでの発作関連のけが，発作自体はスポーツへのかかわりに関係なかったとし，運動を奨励するプログラムが推進されるべきであるとしている．発作の児童の運動への関与は精神的にもよく，社会性，自尊心を高め，自己肯定感を育て，QOLを改善する効果があると考えられる．また，過度ではない精神的な高揚は覚醒度を上げ，発作を抑制する効果もある．

2．予防接種

1994年に予防接種法が改正され，てんかんのある子どもでも現行の予防接種を行えるようになった．同年予防接種ガイドラインが出され，その後何度か改められてきた．2005年の予防接種ガイドラインによるとてんかんの既往のある者に対しての基準が示されている[16]（表4）．

集団生活になると感染症に罹患し発熱する機会が増え，てんかんや熱性けいれんのある子どもでは，けいれんが誘発されることも多い．と

表4　てんかん既往者の予防接種基準（2005年予防接種ガイドライン）

1. コントロールが良好なてんかんを持つ小児では，最終発作から2～3カ月程度経過し，対朝が安定していれば現行のすべてのワクチンを接種しても差し支えない
2. 1．以外のてんかんを持つ小児においてもその発作状況がよく確認されており，症状と体調が安定していれば主治医（接種医）が適切と判断した時期にすべての予防接種をしても差し支えない
3. 発熱によって痙攣発作が誘発されやすいてんかん児（重症ミオクロニーてんかんなど）では，副反応による発熱が生じた場合の発作予防策（ジアゼパム坐剤，経口剤など）と万一発作時の対策を指導しておく
4. ACTH療法後のワクチンは6カ月以上あけて接種する（＊）
5. ガンマグロブリン大量療法（総投与量が約1 g/kg以上）後の生ワクチン（風疹，麻疹，水痘，ムンプスなど）は6ヶ月以上，それ以外の量では3カ月以上あけて接種する（＃）．ただし，接種効果に影響がないワクチン（ポリオ，BCG，DPT，インフルエンザなど）はこの限りでない
6. なお，いずれの場合も事前に保護者への十分な説明と明示の同意が必要である

＊：ACTH後の免疫抑制状態における生ワクチン接種による罹患と抗体獲得不全のリスクは，ACTH投与量，投与方法で差があるので主治医（接種医）の判断でこの時期は変更可能である

＃：接種前3カ月以内に輸血又はガンマグロブリン製剤の投与を受けた者は，本剤の効果が得られない恐れがあるので，3カ月以上過ぎるまで摂取を延期すること．また，ガンマクログロブリン製剤の大量療法，すなわち川崎病，特発性血小板減少性紫斑病（ITP）等の治療において200 mg/kg以上投与を受けた者は，6カ月以上（麻疹感染の危険性が低い場合は11カ月以上）過ぎるまで接種を延期すること

くに，発熱によりけいれん重積になりやすい乳児重症ミオクロニーてんかんでは注意が必要である．このようなことから，各予防接種の副反応の特徴を把握し，とくに発熱時のけいれんに対する万全の対応をとって，積極的に予防接種を行うべきであろう．保護者や本人に予防接種の目的，意義，予想される副反応などについて十分に説明し，納得を得るとともに，発熱，けいれん時の対応を指導する．発熱に気づいたときにはジアゼパムを用いる．坐剤または経口的に 0.4 ～ 0.5 mg/kg/回（最大 10 mg/1 回），発熱持続時は 8 時間後 0.3 ～ 0.4 mg/kg/回（最大 10 mg/回）を追加する．

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Biphasic Clinical Course and Early White Matter Abnormalities may be Indicators of Neurological Sequelae after Status Epilepticus in Children

Abstract

Clinical course and serial neuroimaging findings are not fully described in children who have had neurological sequelae following status epilepticus. We found four patients who had neurological sequelae out of 42 children with status epilepticus in 2004. MRI studies were reviewed with specific attention to diffusion-weighted images (DWI) and the apparent diffusion coefficient (ADC). Proinflammatory cytokines, including tumor necrosis factor-α and interleukin-6, were measured in the cerebrospinal fluid (CSF) (3 patients). The clinical course showed biphasic; initial status epilepticus and neurological exacerbation along with seizure recurrence four to five days after onset. Within three days after initial status epilepticus, CT (all patients) and MRI (2 patients) did not show any abnormalities. From four to ten days after onset, MRI demonstrated diffuse hyperintensity in the cerebral white matter on DWI and hypointensity on ADC maps in all patients. Diffuse brain atrophy progressed thereafter. Tumor necrosis factor-α or interleukin-6 was elevated in all patients. A biphasic clinical course may be a specific feature for neurological sequelae. The preferential white matter involvement on MRI and elevated CSF cytokines indicate that glial dysfunction may play an important role in the pathophysiology of status epilepticus-associated cerebral damage.

Key words
Status epilepticus · children · diffusion-weighted images · ADC maps · white matter · biphasic clinical course

Abbreviations

ADC	apparent diffusion coefficient
CSF	cerebrospinal fluid
DWI	diffusion-weighted image
EEG	electroencephalogram
FLAIR	fluid-attenuated inversion recovery
IL-6	interleukin-6
IV	intravenous
SE	spin-echo
TE	echo time
T_1WI	T_1-weighted image
T_2WI	T_2-weighted image
TNF-α	tumor necrosis factor-alpha
TR	repetition time

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Introduction

Status epilepticus is a common emergency in infants and children and poses a risk for status epilepticus-associated neurological sequelae. Neurological sequelae following status epilepticus have reached 10–20% in recent pediatric series [17,25]. Although there have been many imaging studies dealing with cerebral abnormalities during or following status epilepticus, these were mostly evaluated by conventional CT or MRI, including T_1-weighted images (T_1WI), T_2-weighted images (T_2WI), and fluid-attenuated inversion recovery (FLAIR) images. Cerebral abnormalities associated with status epilepticus usually show hypointensity on CT, hyperintensity on T_2WI and FLAIR image, indicating cerebral edema. A recent advantage of neuroimaging revealed that diffusion-weighted images (DWI) and the apparent diffusion coefficient (ADC) are more sensitive in identifying ischemic cerebral lesions than conventional MRI. DWI and ADC reflect changes in water diffusion and appear useful in distinguishing between cytotoxic edema and vasogenic edema. In the acute stage of ischemic cerebral lesion, hyperintensity on DWI and hypointensity on the ADC map means cytotoxic edema, which is usually followed by cerebral atrophy. Instead, isointensity on DWI despite hyperintensity on T_2WI and FLAIR image means vasogenic edema, which is usually reversible. Therefore, DWI and ADC are superior in identifying cerebral abnormalities and evaluating the pathophysiology of cerebral abnormalities than the conventional neuroimaging. DWI and ADC have been applied in patients with status epilepticus [1,3,4,6,7,9,10,12–15,27]. Researchers have successfully demonstrated cerebral abnormalities similar to ischemia: hyperintensity on DWI and hypointensity on ADC maps were also shown in the epileptogenic area. MRI abnormalities were predominantly located in the gray matter and were mostly transient and reversible [6,12,14,15,27]. Therefore, the gray matter is considered to be more vulnerable to status epilepticus. We report four patients who suffered status epilepticus and developed neurological sequelae, and showed prominent white matter abnormalities on DWI and ADC maps several days after status epilepticus.

Patients and Methods

Study population and design

Tottori University Hospital, Tottori Prefectural Central Hospital, Tottori Prefectural Kousei Hospital, and Matsue Red Cross Hospital serve the whole area of Tottori Prefecture and the eastern part of Shimane Prefecture. All emergency cases of infants and children in this area are referred to these four hospitals. We reviewed the medical records of infants and children aged 1 month to 16 years who were referred to any of these hospitals due to status epilepticus from January to December in 2004. Status epilepticus was defined as any seizure lasting more than 30 minutes or recurrent seizures lasting a total of more than 30 minutes without complete recovery of consciousness. We excluded patients who had status epilepticus due to an acute symptomatic cause such as meningitis, encephalitis, head trauma, cerebrovascular disease, and systemic and metabolic disease. We also excluded patients with specific encephalopathy such as Reye's syndrome, acute necrotizing encephalopathy, and hemorrhagic shock and encephalopathy. The reason is that pathophysiological changes other than status epilepticus strongly affect cerebral injury in these diseases. To identify the possible causes of status epilepticus, a routine laboratory examination including a complete blood count, blood chemistry, serum glucose, urinalysis, cerebrospinal fluid (CSF), cranial CT or MRI, and EEG was performed for each patient. Further metabolic analysis including plasma and urine amino acids, urine organic acids, and blood and CSF lactic acids was performed in patients who showed any neurological sequelae after status epilepticus.

Data acquisition

CT and MRI were reviewed by neuroradiologists (SF, TO). MRI was performed on a 3-T system (Signa Horizon; GE Medical Systems, Milwaukee, WI, USA) or 1.5-T systems (EXCELART, Toshiba, Tokyo, Japan and Signa, GE Medical Systems, Milwaukee, WI, USA). T_1WIs were obtained by the spin-echo (SE) technique with a repetition time (TR) of 450–460 msec and an echo time (TE) of 11–12 msec (450–465/11–12) on the 1.5-T systems. On the 3-T, T_1WIs were obtained by 3D RF-spoiled gradient echo (SPGR) with 9/2/18 (TR/TE/flip angle). T_2WIs were obtained by using a fast SE technique with 4000–4200/83.5–101 (TR/TE). FLAIR images were obtained with 8002–10 002/110–120/1800–2500 (TR/TE/inversion time). Single-shot DWI was performed in the axial projection with 5999–7000/84–110 (TR/TE), low-strength gradient (b: 0 sec/mm^2), and high-strength diffusion gradient (b: 1000 sec /mm^2). The low b value images served as a baseline for comparison with the high b value images. These images were obtained by varying diffusion gradient strength along each of three orthogonal directions. Diffusion trace maps were computed from the isotropic diffusion image. ADC maps were calculated on the basis of these b0 and b1000 images.

Cytokine assay

Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) were measured in CSF using the human chemiluminescent immunoassay kits by R&D systems (Minneapolis, MN, USA). CSF samples were collected from three patients (Patients 1, 2, and 4) after the elimination of initial status epilepticus. A CSF sample was also taken on the fourth day of onset in Patient 1. The normal range of CSF TNF-α was less than 6.2 pg/mL and that of IL-6 was less than 9.7 pg/mL [11].

Results

Fifty status epilepticus episodes in 42 children met the inclusion criteria for the present study. Diagnosis was febrile convulsion for 23 episodes in 23 children, and epileptic seizure for 27 episodes in 19 children. We found four patients who suffered status epilepticus followed by neurological sequelae out of 23 patients with febrile convulsion.

Case reports

Patient 1

A 19-month-old boy was born by Cesarean section due to Chiari malformation. Myelomeningocele and hydrocephalus were recognized and surgical repair was performed early after birth. He required placement of a ventriculoperitoneal shunt at two months of age. His mental and motor development were mildly delayed at 18 months. He had no previous seizures. The patient

was referred to the hospital due to pyrexia for three days and then presented with generalized clonic convulsions. His seizure continued for 25 minutes despite rectal and intravenous (IV) administration of diazepam and IV midazolam. It was ameliorated with IV thiopental but recurred soon. Clinical seizure was then stopped with repeated use of thiopental, while ictal EEG discharges continued in the right occipital region. EEG seizure activity was eventually stopped with rectal administration of phenobarbital. The observed seizure duration including clinical and EEG seizures was 180 minutes.

On admission he was unresponsive with a body temperature of 39.7 °C. Physical examination was unremarkable except for respiratory distress. He showed no meningeal signs. Routine laboratory tests revealed a leukocyte count of 12900/μL and serum CRP levels of 4.0 mg/dL. Other routine laboratory findings were unremarkable. CSF examination was normal. Viral and bacterial cultures were negative in CSF. Metabolic analysis was unremarkable. CT findings were unchanged compared to the previous studies. Sleep EEG showed continuous slow waves in the occipital region. Rectal administration of phenobarbital was maintained to prevent recurrence of seizure. When he became afebrile on the third day of seizure onset, he was still in a semicoma, but sometimes opened his eyes and followed his parent's movements with his eyes. He showed severe hypotonia. A few series of apnea were found. Routine laboratory tests, CSF examination and EEG were repeated and were all unremarkable.

Brief but frequent partial seizures recurred on the fifth day of onset. The seizure was not controllable only with IV thiopental but stopped with continuous IV infusion of midazolam. After the seizure recurrence, he went into a coma and developed choreoathetoid movements bilaterally. A year later, the patient was able to control his head, but was not able to sit without support or speak.

Patient 2

A 13-month-old boy was referred to the hospital due to status epilepticus. He had no previous seizures or neurological illness. His birth was uneventful and his development was normal. His father had febrile convulsions in childhood. He had febrile illness and generalized tonic-clonic convulsions occurred on the same day. When he reached the hospital, his seizure continued for 120 minutes despite a rectal administration of diazepam. IV diazepam and midazolam failed to stop the seizure but it was eventually controlled with IV thiamylal. The clinically observed seizure duration was 150 minutes. On admission, he was unresponsive with a body temperature of 40.6 °C. Physical examination was unremarkable except for respiratory distress. He showed no meningeal signs. Routine laboratory findings were all unremarkable. CSF examination was also normal. Viral and bacterial cultures were negative in CSF. Metabolic analysis was unremarkable. Cranial CT and MRI were unremarkable. Sleep EEG was also unremarkable on the second day. A continuous IV of midazolam and rectal administration of phenobarbital were maintained to prevent recurrence of seizure. On the second day of onset, he was in a semicoma, but sometimes opened his eyes and followed his parent's movements with his eyes. Status epilepticus recurred on the fourth day of onset. The seizure was not controllable only with IV diazepam and midazolam but stopped with continuous IV infusion of thiamylal. After the second status epilepticus, he went into a deep coma. Sleep EEG showed generalized slow waves. When he became afebrile on the sixth day of onset, a small skin rash appeared. Human herpes virus-6 DNA was isolated from the blood by PCR, but not from the CSF. Therefore he was diagnosed with exanthema subitum. The patient then developed choreoathetoid movements bilaterally. A year later, he was able to sit without assistance and follow an object with his eyes, but was not able to walk or reach an object with his hands. He had subtle but daily seizures.

Patient 3

An 18-month-old girl was referred to the hospital due to status epilepticus. She had no previous seizures or neurological illness. Her birth was uneventful and her development was normal. Her uncle had febrile convulsions in childhood. She had febrile illness and right hemi-convulsion on the same day. When she reached the hospital, her seizure continued for 60 minutes despite rectal administration of diazepam. Her seizure was ameliorated with IV diazepam but recurred soon, and was eventually controlled with IV midazolam. The clinically observed seizure duration was 90 minutes. On admission she was unresponsive with a body temperature of 39.3 °C. Physical examination was unremarkable except for respiratory distress. She had motor palsy in the right upper and lower extremities. She showed no meningeal signs. Routine laboratory findings were all unremarkable. CSF examination was also normal. Viral and bacterial cultures were negative in CSF. Metabolic analysis was unremarkable. Cranial CT was unremarkable. IV midazolam and rectal administration of phenobarbital were maintained to prevent recurrence of seizure. On the second day of onset, she was in a semicoma, but sometimes she opened her eyes and followed her parent's movements with her eyes. She showed hemiparesis and hemianopsia on the right side. On the fourth day of onset, she went into a deep coma and MRI abnormalities were evident. Repetitive clonic convulsions of the right side of the body recurred on the fifth day of onset. The seizure was not controllable with IV midazolam and phenytoin but was stopped with continuous IV infusion of thiamylal. She then developed transient tremorous movements bilaterally. A year later, she was severely mentally retarded with right hemiparesis and right hemianopsia, and intractable epilepsy. She was able to sit without assistance and follow an object with her eyes, but was not able to walk or reach an object with her hands.

Patient 4

A 12 month-old boy was referred to the hospital due to status epilepticus. He had no previous seizures or neurological illness. His birth was uneventful and his development was normal. He had febrile illness and generalized tonic-clonic convulsion occurred on the next day. When he reached the hospital, his seizure continued for 120 minutes despite IV administration of diazepam. The seizure was eventually controlled with the additional usage of diazepam and phenobarbital. The seizure duration ultimately reached 150 minutes. On admission he was unresponsive with a body temperature of 39 °C. He showed no meningeal signs. Routine laboratory findings were all unremarkable. CSF leukocyte count was 16/mm^3 (33% polynuclear leukocytes and 67% mononuclear leukocytes) and normalized on the next day. Viral and bacterial cultures were sterile in CSF. Metabolic analysis was un-

Table 1 Summary of CT and MRI findings

	Hyperacute (days 1–3)	*Acute (days 4–10)*	*Subacute (days 11–30)*	*Chronic (day 31 onwards)*
Clinical state	semicoma	deep coma, seizure recurrence	improving	improving, mental retardation
Global CT/MRI findings	unremarkable (4/4)	mild brain swelling (4/4)	diffuse brain atrophy (4/4)	progressive atrophy (3/3)
CT	unremarkable (4/4)	loss of gray-white junction (3/3), diffuse low density (2/3)	loss of gray-white junction (2/3), diffuse low density (2/3)	
T_2WI/FLAIR	unremarkable (2/2)	linear hyperintensity in the gray-white junction (3/4) Diffuse cortical hyperintensity (2/4)	→ resolved(3/3); diffuse cortical hyperintensity (2/3) localized hyperintensity (3/3) (gray matter 1, white matter 2)	diffuse cortical hyperintensity (1/2) localized cortical hyperintensity(1/2)
Restricted diffusion on DWI and ADC maps	none (2/2)	white matter (4/4, diffuse 2, subcortical 2)	→ resolved (3/3), gray matter (localized, 1/3)	none (2/2)

remarkable. CT showed no abnormal findings. EEG demonstrated generalized slow waves. Rectal administration of phenobarbital was maintained to prevent recurrence of seizure. On the second day of onset, he was in a semicoma, but sometimes opened his eyes and followed his parent's movements with his eyes. The patient went into a coma on the fourth day of onset and the seizure recurred on the fifth day of onset. The generalized or focal clonic seizures repeated despite initiation of phenytoin and carbamazepine and eventually stopped on the next day. Six months later, when he was 18 months old, he was able to sit alone, but was not able to walk or speak. His developmental quotient was 46.

Imaging findings

CT and MRI were analyzed at different stages following status epilepticus. The hyperacute stage was within three days after the onset of status epilepticus. All patients gradually improved following status epilepticus but were still in a semicoma in this stage. CT was performed just after cessation of status epilepticus in all patients. MRI was performed in two patients. The acute stage was from the fourth to the tenth day of onset. All patients went into a deep coma and had a recurrence of seizures in this stage. MRI was performed on all patients. The subacute stage was from the 11th to the 30th day of onset. All patients started to improve after exacerbation in this stage. The chronic stage was after the 30h day of onset. All patients were still improving but neurological sequelae were evident in this stage. The changes of ADC values were examined in Patient 1. Table **1** shows a summary of the neuroimaging findings.

Patient 1

Hyperacute stage (Fig. **1 A**): Neither brain swelling nor abnormal signal suggesting status epilepticus was found on CT (day 1) and MRI (day 3).

Acute stage (Fig. **1 B**): CT (day 5) showed loss of gray-white junction diffusely in the cerebrum. MRI (day 7) showed gyral swelling and subtle linear hyperintensity in the gray-white junction on T_2WI and FLAIR image. DWI revealed symmetrical hyperintensities in the cerebral white matter, whereas such abnormalities were not conspicuous on T_2WI and FLAIR images. ADC maps showed restricted diffusion in the cerebral white matter.

Subacute stage (Fig. **1 C**): Enlargement of the lateral ventricle and widening of the cortical sulci suggesting diffuse brain atrophy were present. Diffuse white matter hyperintensities disappeared on DWI (day 22). Hyperintensities in the bilateral occipital white matter became conspicuous on FLAIR images. Their adjacent gray matter appeared mildly hyperintense on DWI. The ADC maps showed restricted diffusion in the corresponding occipital gray matter.

Chronic stage: On the 2-month follow-up CT, progressive brain atrophy was clear as compared with images of the subacute stage.

Changes of ADC values ($\times 10^{-3}$ mm^2/s): The ADC values of the frontal gray matter at the hyperacute, acute, and subacute stages were 1.13, 1.05, and 1.23, respectively. Those of the frontal white matter were 0.80, 0.31, and 0.81, respectively. The ADC values of the occipital gray matter were 1.06, 0.83, and 0.74, respectively. Therefore, the decrease of the ADC values was 61% in the frontal white matter at the acute stage and 30% in the occipital gray matter at the subacute stage.

Patient 2

Hyperacute stage (Fig. **2 A**): CT (days 1 and 3) showed no abnormal findings. Neither brain swelling nor abnormal signal intensity was found in any MR image (day 2).

Acute stage (Fig. **2 B**): T_2WI and FLAIR image (day 6) showed blurring of the gray-white junction in the cerebral hemisphere, especially in the frontal lobe. Extensive gyral hyperintensity and subtle linear hyperintensity in the gray-white junction were also observed. DWI clearly revealed symmetrical hyperintensities in the periventricular and subcortical white matter. The ADC maps showed restricted diffusion in these areas. Gyral swelling was not found.

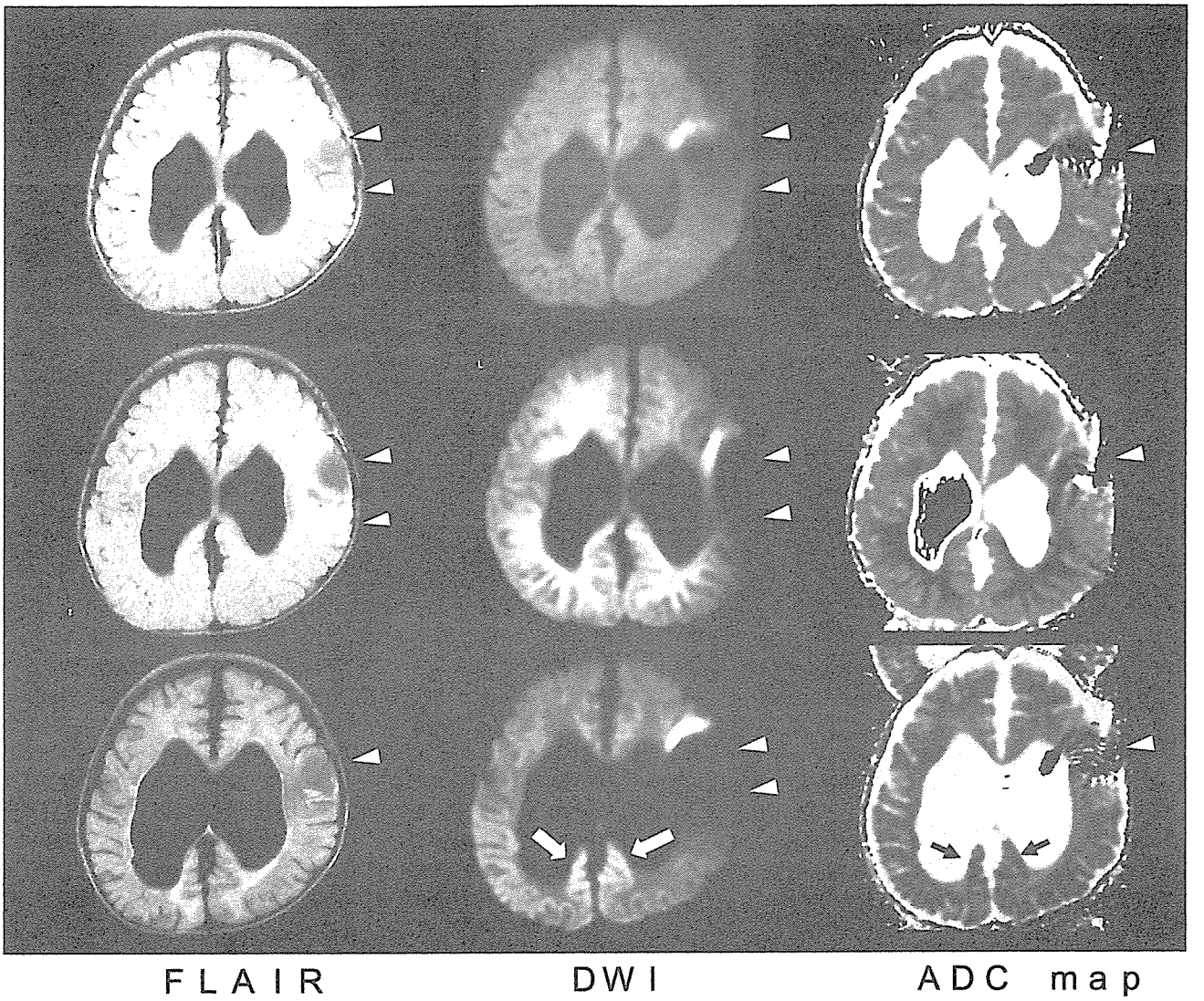

Fig. **1** Fluid-attenuated inversion recovery (FLAIR) images, diffusion-weighted images (DWI), and apparent diffusion coefficient (ADC) maps of Patient 1 at the hyperacute (**A**), acute (**B**), and subacute stages (**C**) following status epilepticus. Significant dilatation of lateral ventricles due to Chiari malformation can be seen on all MRIs. (**A**) Neither brain swelling nor abnormal signal intensity is found in the hyperacute stage. (**B**) Cerebral white matter shows symmetrical hyperintensities on DWI and hypointensities on ADC maps in the acute stage. (**C**) White matter hyperintensities disappeared on DWI and diffuse brain atrophy progressed in the subacute stage. Bilateral occipital gray matter shows mild hyperintensities on DWI and hypointensities on ADC map (arrow). A shunt valve artifact is seen in the left frontoparietal region (arrowhead).

Subacute stage (Fig. **2C**): MRI (day 15) showed mild diffuse brain atrophy. Diffuse white matter hyperintensities disappeared on DWI. DWI also showed mild hyperintensity in the left temporo-occipital region. However, restricted diffusion was not apparent in this area on the ADC maps.

Chronic stage (Fig. **2D**): T_2WI and FLAIR images showed progression of marked brain atrophy and localized periventricular hyperintensity on the 1-month follow-up MRI. FLAIR image and DWI showed mild hyperintensity of the cerebral cortices.

Patient 3

Hyperacute stage: CT (day 1) showed no abnormal findings.

Acute stage (Fig. **3A**): MR images (day 4) showed diffuse swelling of the left cerebral hemisphere. Subtle linear hyperintensity was also seen in the gray-white junction on T_2WI and FLAIR images. While mild hyperintensities in the periventricular and subcortical white matter were recognized on T_2WI and FLAIR images, these abnormalities were more conspicuous on DWI. The ADC maps showed restricted diffusion in these areas.

Subacute stage (Fig. **3B**): MR images (day 26) showed moderate diffuse brain atrophy and residual hyperintensities in the subcortical and periventricular white matter of the left temporal, parietal, and occipital lobes on the T_2WI and the DWI. The ADC maps also showed hyperintensities in the corresponding areas. Hyperintensity on DWI in these areas was due to T_2 shine-through.

Chronic stage: MR and CT images were not available.

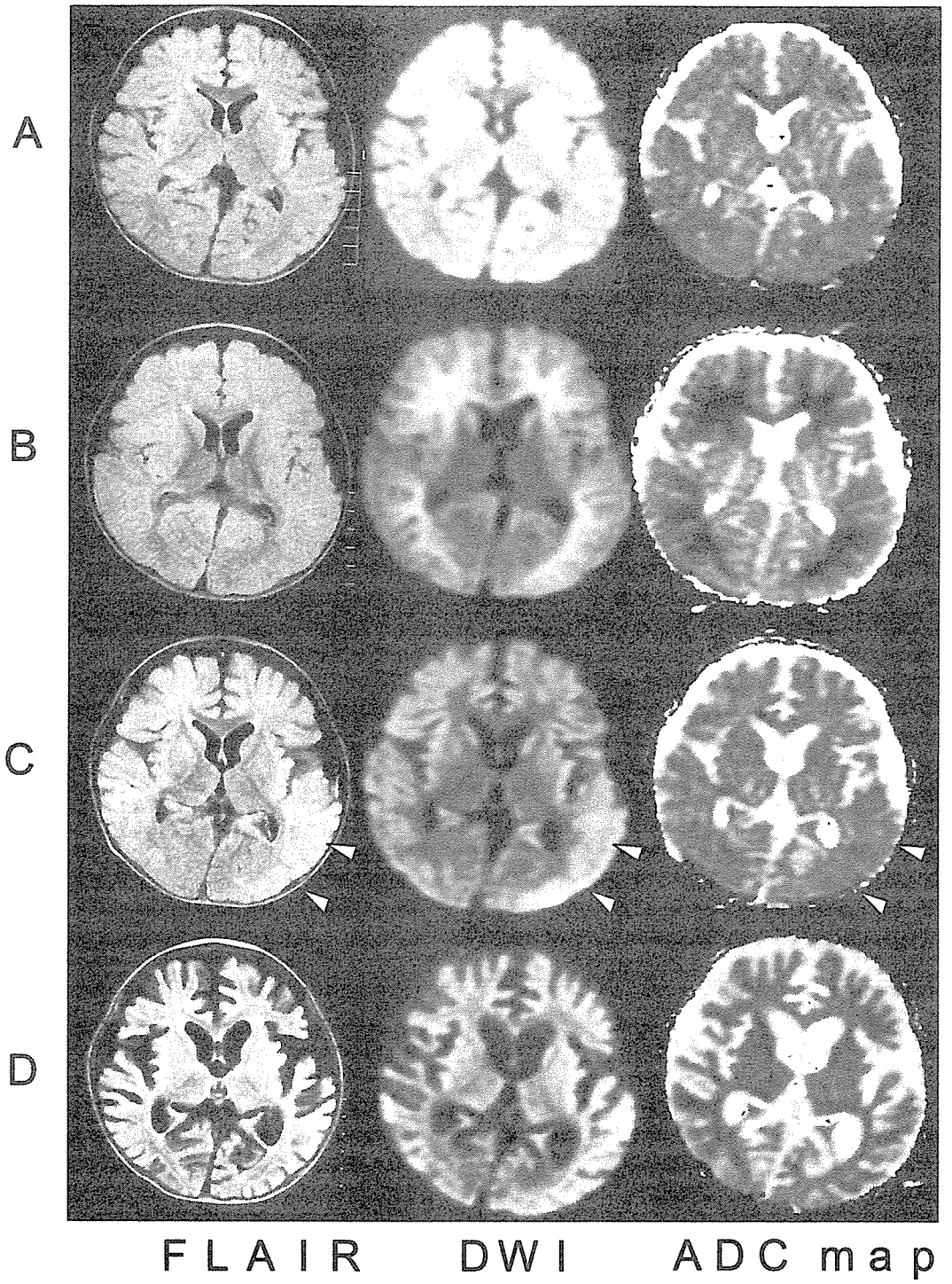

Fig. 2 Fluid-attenuated inversion recovery (FLAIR) images, diffusion-weighted images (DWI), and apparent diffusion coefficient (ADC) maps of Patient 2 at the hyperacute (**A**), acute (**B**), subacute (**C**), and chronic stages (**D**) following status epilepticus. (**A**) Neither brain swelling nor abnormal signal intensity is found in the hyperacute stage. (**B**) Cerebral white matter shows symmetrical hyperintensities on DWI and hypointensities on ADC map in the acute stage. (**C**) White matter hyperintensities disappeared on DWI in the subacute stage. The left temporo-occipital region shows mild hyperintensity on FLAIR image and DWI (arrowhead). The ADC map shows no abnormal signals in the corresponding areas. (**D**) Diffuse brain atrophy progressed in the chronic stage.

Patient 4

Hyperacute stage: CT (days 1 and 3) showed no abnormal findings.

Acute stage (Fig. **4A**): CT (days 5 and 6) demonstrated loss of gray-white junction in the cerebrum. DWI (day 6) revealed symmetrical hyperintensities in the centrum semiovale, whereas no definite abnormalities were detected on T_2WI and FLAIR images. The ADC map showed restricted diffusion in the centrum semiovale.

Subacute stage: Enlargement of the lateral ventricle and widening of the cortical sulci, suggesting diffuse brain atrophy was present on CT (day 15).

Chronic stage (Fig. **4B**): The 2-month follow-up MRI showed disappearance of white matter abnormalities and progression of brain atrophy with diffuse widening of cortical sulci.

CSF cytokines (Table 2)

IL-6 or TNF-α was elevated in each patient. IL-6 was elevated in all patients and TNF-α was elevated in Patients 1 and 2.

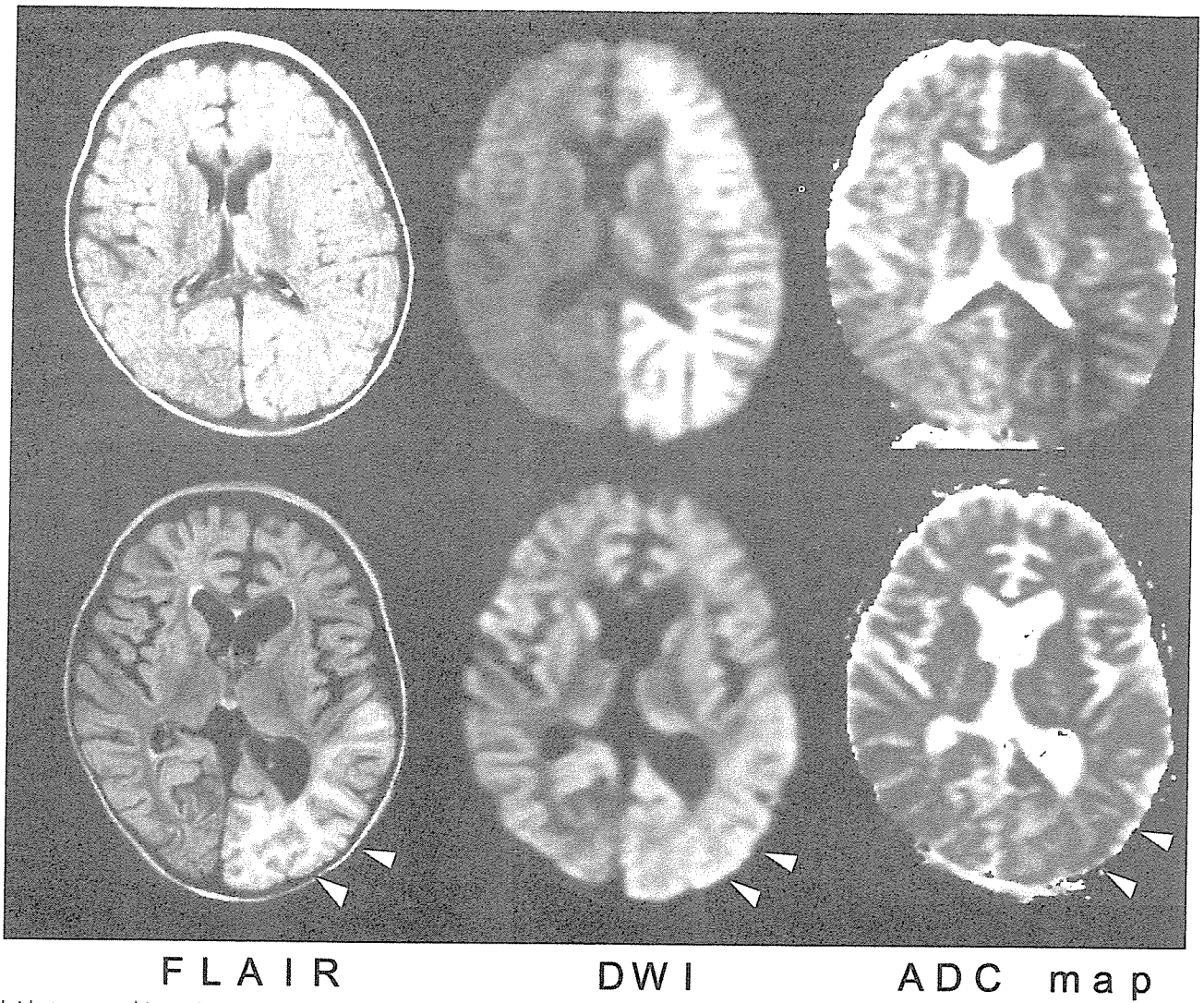

Fig. 3 Fluid-attenuated inversion recovery (FLAIR) images, diffusion-weighted images (DWI), and apparent diffusion coefficient (ADC) maps of Patient 3 at the acute (**A**) and subacute stages (**B**) following status epilepticus. (**A**) Cerebral white matter of the left hemisphere shows hyperintensities on DWI and hypointensities on ADC map in the acute stage. (**B**) MR images show moderate diffuse brain atrophy and residual hyperintensities in the white matter of the left temporal, parietal, and occipital lobes on the FLAIR image and DWI (arrowhead). The ADC map also shows hyperintensities in the corresponding areas (arrowhead).

Other children who had no neurological sequelae after status epilepticus

Seizure duration ranged from 30 to 180 minutes (mean: 52.0, standard deviation: 21.8). In patients with febrile convulsion, seizure duration ranged from 30 to 60 minutes (mean: 42.4, standard deviation: 13.1): seizure duration was significantly longer in the four patients with neurological sequelae than in patients without neurological sequelae ($p = 0.002$, Wilcoxon test). None of the children showed neurological exacerbation or seizure recurrence several days after initial status epilepticus.

Discussion

The most striking neuroimaging findings observed early after status epilepticus in the present patients were hyperintensity on DWI and hypointensity on ADC maps in the white matter. In most previously reported cases, DWI hyperintensity and ADC hypointensity were located dominantly in the restricted gray matter during or early after status epilepticus [4,6,12,14,15 27]. White matter abnormalities on DWI were reported in a few cases [1,7,9,13,14]. Because we experienced four patients who had neurological sequelae out of 42 children with status epilepticus in our hospitals and they all showed pronounced white matter abnormalities on MRI, preferential white matter abnormalities after seizures may not be rare. DWI and ADC maps clearly demonstrated white matter abnormalities while other conventional imaging techniques including FLAIR images failed to detect these findings. As evaluation by DWI and ADC maps has not been routinely performed until a few years ago in Japan, white matter abnormalities could have previously been missed. Moreover, the DWI and ADC abnormalities were only recognized in the restricted periods following status epilepticus (from four to ten days after onset). Hence, white matter abnormalities would be common findings soon after status epilepticus, when cerebral damage permanently occurs.

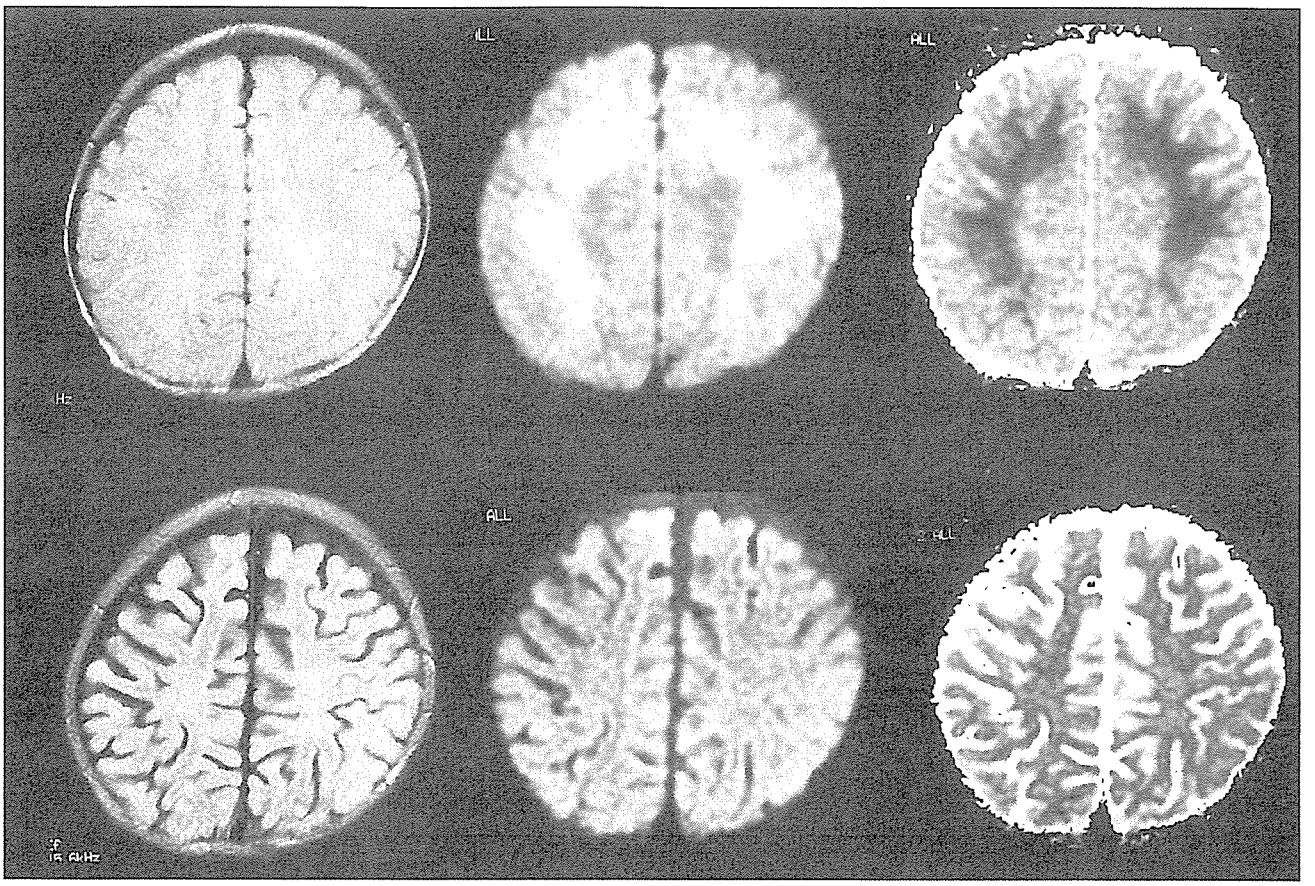

Fig. 4 Fluid-attenuated inversion recovery (FLAIR) images, diffusion-weighted images (DWI), and apparent diffusion coefficient (ADC) maps of Patient 4 at the acute (**A**) and chronic stages (**B**) following status epilepticus. (**A**) DWI shows symmetrical hyperintensities in the subcortical white matter and centrum semiovale in the acute stage. The ADC map shows hypointensities in the corresponding region. (**B**) White matter hyperintensities disappeared on DWI and diffuse brain atrophy progressed in the chronic stage.

The preferential white matter involvement on MRI similar to the present patients has been reported in anoxic-ischemic encephalopathy [2]. Chalela et al. reported seven cases with prominent white matter abnormalities seen on DWI within 7 days after anoxic-ischemic events. High DWI and low ADC were symmetrically and diffusely found in the white matter. In the rat model, oligodendrocyte and astrocyte injury preceded neural injury following ischemia [22]. Medelcu et al. reported biphasic edema after hypoxic-ischemic injury in neonatal rats [21]. The early edema reflected neuronal death and the second edema was associated with glial damage. Severe hypoxemia which directly induced cerebral injury was not present in our patients, indicating that white matter injury can also occur early after status epilepticus. In the pathological study of the human brain of influenza encephalopathy, clinically characterized by prolonged seizure and consciousness disturbance followed by significant brain edema. Nakai et al. found that microglial activation was observed in the gray and white matter and astroglial activation was seen in the white matter [20]. The elevated CSF cytokine levels found in the present patients indicate an activation of glial function. In the rat brain, glial activation and swelling were shown early after status epilepticus [5,23,24]. Glial fibrillary acidic protein levels were elevated in the CSF from patients with status epilepticus [8]. Therefore, prolonged seizure activity can induce glial activation similar to global hypoxia. Glial hyperfunction or hypofunction may lead to the induction of proinflammatory cytokines or nitric oxide, release of excitatory amino acids, or blood-brain barrier breakdown, resulting in both glial and neural injury.

Another possibility for the white matter diffusion abnormality is acute axonal injury due to diffuse cortical damage [18,26]. Watanabe et al. studied axonal function in patients with brain death using anisotropic DWI [26]. They reported that diffusion anisotropy started to decrease 1 to 12 hours and reached isotropy 24 to 44 hours after the onset of brain death. Therefore, restricted diffusion in the white matter may reflect delayed axonal dysfunction secondary to diffuse cortical injury.

One might expect that the white matter abnormalities seen in the acute stage were caused by second seizures four to five days after onset. But this is unlikely, because CT and MRI abnormalities preceded seizure recurrence in Patients 3 and 4. White matter abnormalities could primarily be a consequence of the first status epilepticus. Such delayed imaging findings following status epilepticus were reported in a few cases without seizure recurrence [9,19]. Nevertheless, seizure recurrence might affect further cerebral injury.

Table 2 Clinical characteristics, CSF findings, and prognosis

	Age (months) /sex	Prior neurological disorder	Initial seizure duration (min)	Second seizure		CSF (days of collection)			Prognosis
				Days of onset	Duration (h)	Cell[a]/Protein[b]/Sugar[c]	IL-6[d]	TNF-α[d]	
Patient 1	19/M	Chiari II malformation hydrocephalus, mild developmental delay	180 (lasting)	5	26 (repetitive)	0/3.1/86 (1), 1/1.4/79 (4)	2.3 (1), 10.8 (4)	68.4 (1), 56.6 (4)	severe MR
Patient 2	13/M	none	150 (lasting)	4	1 (lasting)	0/23/134 (1)	12.5 (1)	1041.8 (1)	severe MR
Patient 3	18/F	none	90 (lasting)	5	50 (repetitive)	0/20/130 (1)	NE	NE	severe MR, right hemiparesis
Patient 4	12/M	none	150 (lasting)	5	24 (repetitive)	16/15.4/190 (1)	70.9 (1)	ND (1)	moderate MR

[a]/mm^3; [b]mg/dL; [c]mg/dL; [d]pg/mL; F = female; M = male; MR = mental retardation; ND = not detectable; NE = not examined; h = hour; min = minutes

In the subacute and chronic stages, the DWI hyperintensity seen in the white matter at the acute stage resolved, and ADC hypointensity became isointense and then hyperintense. At the same time, T_2 and FLAIR hyperintensity became apparent in both white and gray matter, and diffuse brain atrophy progressed. These signal changes possibly reflect cell damage and gliosis. At the subacute stage in Patient 1, DWI hyperintensity and ADC hypointensity were seen in the occipital cortex, while they were isointense in the hyperacute and acute stages. This highly delayed cytotoxic edema is peculiar and may be secondary to white matter injury.

The clinical course early after status epilepticus has not been well described previously. Other than the present patients, a detailed clinical course was described in a few patients with hemiconvulsion-hemiplegia syndrome [9,13,19]. Their clinical course and imaging findings were quite similar: initial seizures were prolonged and neurological findings were exacerbated along with seizure recurrence several days later. MRI abnormalities were evident at the time of neurological exacerbation. The present patients also showed a biphasic clinical course. Other children in the present study who had no neurological sequelae after status epilepticus showed no biphasic clinical course. Therefore, a biphasic clinical course may be a specific feature and could be a hallmark for neurological sequelae.

The prognosis of status epilepticus varies widely in each patient. We cannot explain why cerebral damage occurs in some but not all patients after status epilepticus. In the present study, patients who had neurological sequelae were all febrile and their initial seizures were significantly prolonged. Pyrexia and seizure duration would be important factors for status epilepticus-associated cerebral injury [16].

To identify the pathophysiology of status epilepticus-associated cerebral injury and protect against cerebral damage, a prospective and systemic study that includes serial imaging and an analysis of CSF cytokines and other cytotoxic substances is essential.

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