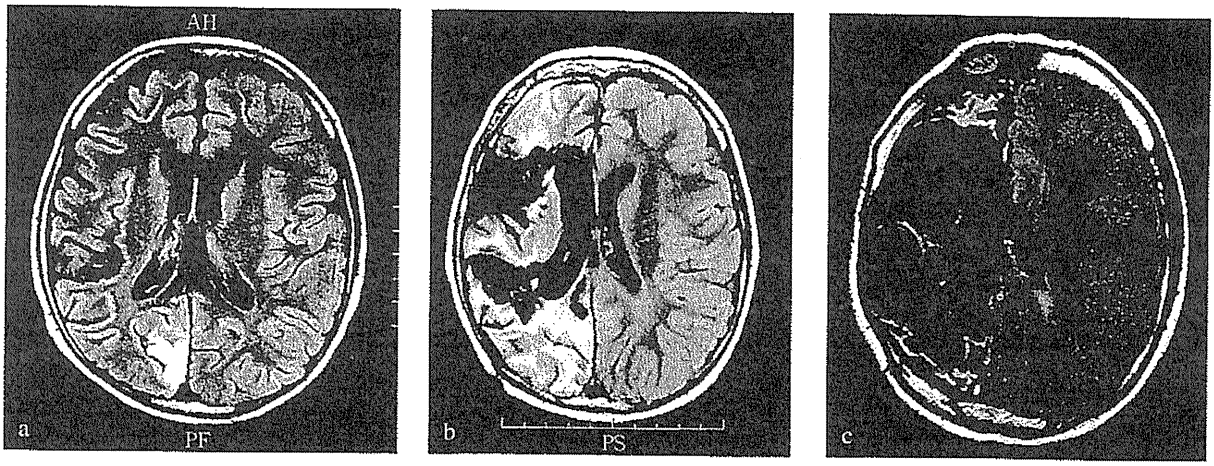

図1 頭部MRI（症例1;FLAIR画像）
a：6歳8カ月（発症より1年5カ月，手術2カ月前）．進行性の右半球萎縮と右後頭葉に一部高信号．
b：7歳5カ月（術後6カ月後）
c：12歳2カ月（術後5年後）

表1 3症例における術後の発作，精神・運動機能の評価

	症例1	症例2	症例3
最終発作	4カ月	1年	術前まで
抗けいれん薬の中止	5年	3年	漸減中
健側半球での安静覚醒時のα波の出現時期	4年	2カ月	2カ月
補助具での歩行	2カ月	1カ月半	5カ月
自立歩行	6カ月	1年半	1年半
学校への復帰	4カ月	4カ月	2カ月

局して健側に波及することはなかった．術後4年で健側半球に8 Hzのα波が持続的に出現するようになった（表1）．術後半年間は嘔気を訴える前兆発作（数秒持続）が一時的に残存したが，それ以降は，てんかん発作は完全に消失した．術後5年で抗てんかん薬はすべて中止できた．

知能検査では，術前の半年間で総知能指数（total intelligence quotient；TIQ）が85から69へ低下していた．しかし，術後のそれは70台を維持している（図2）．粗大運動機能の経過は良好であった．術直後には左下肢の随意運動がかろうじて可能で，左上肢は弛緩性麻痺のためほとんど動かなかった．理学療法により，術後2カ月で体幹や両手を支えれば歩行可能になり，左上肢も前腕のみ挙上できるようになった．術後3カ月で，補助具なしで歩行できるようになり，手すりを使用すれば階段昇降が可能になった．日常生活は自立し，術後4カ月で普通小学校に復帰した．術後の頭部MRIでは，患側半球の進行性萎縮が確認された（図1b，c）．現在，術後8年経過したが，退行はなく，中学校は特別支援学級に通学している（図3）．

症例2 12歳女児

家族歴・既往歴 特記すべきことなし

現病歴 7歳2カ月，上気道炎の3日後に一過性の意識消失発作で発症した．9歳0カ月から左半身の間代発作が出現し，その後数カ月で，EPCと左片麻痺を認めるようになった．免疫グロブリン，ステロイド大量療法を施行するも左上下肢のEPCは覚醒中にも常時出現するようになり坐位保持困難，構音障害を認めるようになった．そのため，9歳8カ月に機能的半球切除術を施行した．術直後は，てんかん発作が消失したが，術後4カ月頃から短時間の嘔気発作が出現し，1～2カ月の周期で再燃増悪を繰り返した．患側の右大脳半球では，発作発射放電を頻回に認めたが，健側の左大脳半球には独立したてんかん発作波は認めなかった．そして，この間も健側の背景脳波は改善し，術前は4 Hzであったものが術後2カ月で7-8 Hzまで回復した．嘔気発作は持続したため，術後1年目に右前頭弁蓋，島回，側頭弁蓋の皮質切除術を追加した．その後の経過は良好で，嘔気発作は消失し，機能的半球切除術後3年目で，抗てんかん薬はすべて中止できた．

知能検査では，術前4カ月でTIQは76から71へと低下し，特に言語性知能指数（verbal IQ；VIQ）が103から89へ低下していた．術後，TIQは75，VIQは94で退行の進行はなかった．（図2）．運動機能は理学療法を継続し，精神的葛藤を経て以下のような経過で回復した．術直後は完全片麻痺の状態で，手術により運動機能が速やかに回復すると思っていた患児にとって大きな精神的負担となり，精神的に鬱状態となった．そのため理学療法のみならず，診察にも抵抗するよ

うになった．心理カウンセリングにより，その後は意欲的に理学療法に取り組むようになった．術後1カ月で座位可能，1カ月半で歩行器を使用しての移動機能を獲得した．術後1年半経過し，補助具なしでの歩行が可能になった．しかし，上肢の運動麻痺に関しては，術後1年以上経過しても，左上肢は肩までしか挙がらず，肘関節の伸展も不可能で，指の動きはほとんど認めていない．術後4カ月で普通小学校にサポートつきで復帰し，現在は普通中学校に通っており，普通高校への通学を希望し，勉学に励んでいる．

症例3　12歳女児

家族歴・既往歴　特記すべきことなし

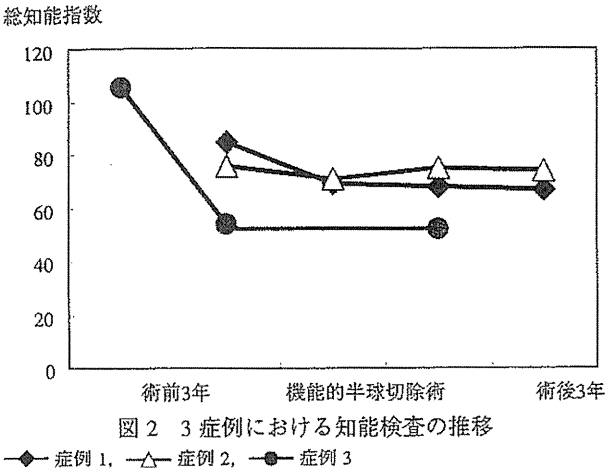

図2　3症例における知能検査の推移

現病歴　6歳1カ月にインフルエンザに罹患し，6歳7カ月から眼瞼や口唇周囲のミオクローヌスが出現し，集中力低下，易刺激性など性格変化を認めた．6歳8カ月には意識変容のない左半身けいれんを認め，次第に頻度が増加した．各種抗てんかん薬，免疫グロブリン大量療法，経口ステロイド，tacrolimus hydrate投与，ケトン食療法などを行ったが，9歳10カ月には発作頻発のため歩行困難となった．術前の知能検査では3年間で105から54へ明らかな低下を認めた（図2）．10歳8カ月にはEPCと左片麻痺のため，かろうじて支持座位を維持できるのみの状態となったため，機能的半球切除術を行った．

術後，発作は消失した．術後5カ月には，装具を使用し歩行可能になり，性格的にも易刺激性が消失した．現在，術後2年が経過し，ステロイドを中止し，最大8種類まで使用していた抗てんかん薬を2剤まで漸減した．発作の再燃はなく，抗てんかん薬によると思われる眠気が激減し，覚醒度が著明にあがり，臨床的に認知能力は上昇した．術前後1年の知能検査は同等で，知能低下の進行を防ぐことはできた．左短下肢装具にて自立歩行可能になり，上肢麻痺は大きな改善はないが，肩関節，肘関節は徒手筋力検査で4/5程度の筋力に回復した．

以上3例とも発表に際し，家族からの承諾を得た．

Ⅱ　考　　察

REの病期については片麻痺の固定などを参考に3段階に分類されている[2]．3症例ともEPCが加わり片麻痺の増悪す

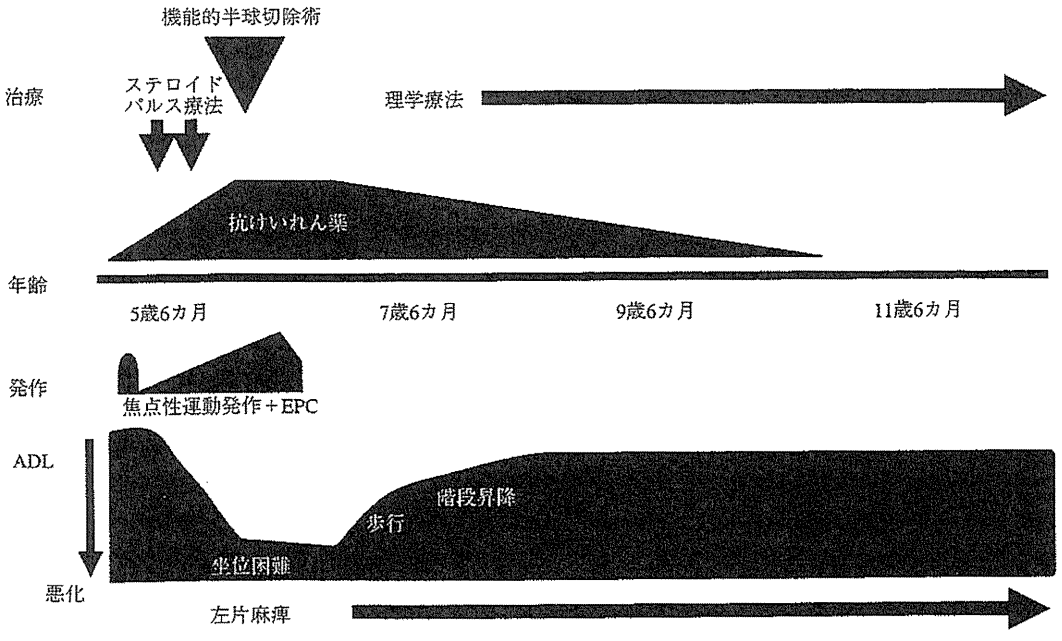

図3　症例1の臨床経過

ADL：activities of daily living，日常生活活動

EPC：epilepsia partialis continua，持続性部分てんかん発作

る Stage 2 まで進行していた．頻回の一側性部分運動発作，EPC のために日常会話が困難なほどの構音障害，座位，歩行も不能な粗大運動の深刻な退行を認めていた．片麻痺については，固定しているのか，頻回の発作のため麻痺しているのかの判別は困難であった．一般的に RE の焦点性感覚・運動発作は，寛解・増悪を繰り返し，免疫療法の効果が一時的に期待できるが，EPC は治療抵抗性で抑制困難とされている[8]．3 例ともに免疫療法にも抵抗性で絶えず顔面，患側上下肢に EPC を認めており，座位保持すら困難であった．そのため半球切除術の適応があると判断された．RE では一側半球の一部より脳炎が時間とともに進行拡大していくとされ，手術時期が早ければその後遺症は大きいものの健側半球の機能は保たれるし，遅くなればその逆となる．今回の 3 例における術後の経過をみると，健側半球の機能は十分保たれていると判断された．機能的半球切除術では，手術直後は上肢を主体に半身麻痺が出現するが，理学療法により次第に麻痺は改善する．特に，下肢の機能は一側大脳半球から両側支配されているので，場合によっては，補助具が必要となるが，訓練すれば歩行は可能になる[9]．しかし，上肢の機能は回復が悪く，指や手首には強い運動機能障害が残るとされている[10]．このことから，RE の半球切除術の適応として片麻痺の固定，つまり，患側の手指の独立した動きができなくなった時点とされており，この機能が保たれている場合には，半球切除術の施行は躊躇される．

3 症例とも片麻痺は残存するものの，日常生活で自立するまで回復した（表 1）．また，術後 6 カ月から 1 年半，平均 1 年 2 カ月で自立歩行可能となり，学校生活には平均 3 カ月で復帰可能となった．術前は進行性に認知力が低下し，特に発作頻度が増え，片麻痺が顕著化し始めると知能指数の低下は急激であった．手術直前の知能検査では以前の検査との間隔が短いため，本来なら学習効果により IQ が上昇することを考慮すれば，片麻痺が進行して不利な状況下での検査であっても，有意な IQ 低下と考えられた．このように術前は急激な IQ 低下を認めたが，術後はさらなる低下はなかった．3 症例とも病期は Stage 2 であり，知的退行はまだ進行すると考えられ，機能的半球切除により知的退行は阻止された．片麻痺の合併のため，VIQ より動作性知能指数（performance IQ ; PIQ）は術前後とも低値であった．脳波所見も術後に改善した．特に症例 2 では，機能的半球切除術後に嘔吐発作を認めていたが，健側に独立したてんかん波はなく，基礎波の遅波化を認めた．

ただし，今回は 3 例とも患側半球が非優位半球であり，幸い術前に言語機能についての詳細な評価の必要性を認めなかった．優位半球側の RE では言語中枢の健側への移動を確認できないと大きな言語障害を残す可能性があり，日常生活活動（activities of daily living ; ADL）が低下しても，必ずしも早急に機能的半球切除術ができるわけではない[11]．

RE は小児期の進行性破局てんかんの代表的なもののひとつであるが，病状が進行すれば機能的半球切除術で恒久的な改善も期待されうる．新たな治療法が開発されるまでは免疫療法で発作，ADL の改善が得られず，片麻痺が固定してきた場合，早期に機能的半球切除術を考慮すべきと考えられた．

機能的半球切除術を行った RE の 3 例を報告した．外科治療により術前に比し，劇的な発作，精神神経学的な改善を得た．RE は緩徐進行性の疾患であり，免疫療法で発作，ADL の改善が得られず，片麻痺が固定してきた場合，早期に機能的半球切除術を考慮すべきと考えた．

文　献

1) Rasmussen T, Olszewski J, Lloyd-Smith D. Focal seizures due to chronic localized encephalitis. *Neurology* 1958;**8**:435-45.
2) Oguni H, Andermann F, Rasmussen T. The natural history of the syndrome of chronic encephalitis and epilepsy: a study of the MNI series of forty-eight cases. In: Andermann F, ed. *Chronic encephalitis and epilepsy: Rasmussen's syndrome.* Boston: Butterworth-Heinemann, 1991:7-35.
3) Muto A, Oguni H, Takahashi Y, et al. Nationwide survey (incidence, clinical course, prognosis) of Rasmussen's encephalitis. *Brain Dev* 2010;**32**:445-53.
4) Bien CG, Granata T, Antozzi C, et al. Pathogenesis, diagnosis and treatment of Rasmussen encephalitis a European consensus statement. *Brain* 2005;**128**:454-71.
5) Terra-Bustamante VC, Machado HR, dos Santos Oliveira R, et al. Rasmussen encephalitis: long-term outcome after surgery. *Childs Nerve Syst* 2009;**25**:583-9.
6) Devlin AM, Cross JH, Harkness W, et al. Clinical outcomes of hemispherectomy for epilepsy in childhood and adolescence. *Brain* 2003;**126**:556-66.
7) Vining EP, Freeman JM, Pillas DJ, et al. Why would you remove half a brain? The outcome of 58 children after hemispherectomy—the Johns Hopkins experience: 1968 to 1996. *Pediatrics* 1997;**100**:163-71.
8) Bien CG, Schramm J. Treatment of Rasmussen encephalitis half a century after its initial description: promising prospects and a dilemma. *Epilepsy Res* 2009;**86**:101-12.
9) Kossoff EH, Vining EP, Pillas DJ, et al. Hemispherectomy for intractable unihemispheric epilepsy etiology vs outcome. *Neurology* 2003;**14**:887-90.
10) Van Empelen R, Jennekens-Schinkel A, Buskens E, Helders PJ, van Nieuwenhuizen O; Dutch Collaborative Epilepsy Surgery Programme. Functional consequences of hemispherectomy. *Brain* 2004;**127**:2071-9.
11) Boatman D, Freeman J, Vining E, et al. Language recovery after left hemispherectomy in children with late-onset seizures. *Ann Neurol* 1999;**46**:579-86.

Three Children with Rasmussen Encephalitis Showing Marked Improvement in Daily Life Activity after Functional Hemispherectomy

Mutsuki Shioda, MD, Hirokazu Oguni, MD, Yasushi Ito, MD, Taku Ochiai, MD, Tomokatsu Hori, MD, Ayako Muto, MD, Satoru Takahashi, MD, Akie Miyamoto, MD, Hitoshi Osaka, MD and Makiko Osawa, MD

Departments of Pediatrics (MS, HO, YI, AM, MO) and Neurosurgery (TO, TH), Tokyo Women's Medical University, Tokyo; Department of Pediatrics, Tokyo Women's Medical University Yachiyo Medical Center, Yachiyo, Chiba (AM); Department of Pediatrics, Asahikawa Medical College, Asahikawa, Hokkaido (ST); Department of Pediatrics, Asahikawa Habilitation Center for Disabled Children, Asahikawa, Hokkaido (AM); Department of Neurology, Kanagawa Children's Medical Center, Yokohama, Kanagawa (HO)

We investigated seizure, intelligence quotient (IQ), and neurological outcomes including the process of motor function recovery after functional right hemispherectomy in 3 children with Rasmussen's encephalitis (RE). Before the procedure, they were unable to walk, nor sit without support due to progressive worsening of left hemiplegia and relentless epilepsia partialis continua (EPC) of the left extremities, which were refractory to antiepileptic drug and immunological treatment. After functional right hemispherectomy, EPC completely disappeared, although complete left hemiplegia was sustained. However, they recovered up to being able to walk independently with assistance devices, and to have an ordinary life with family support within 1.5 to 5 months through rehabilitation. At the same time, the interictal EEG improved on the unaffected side of hemisphere, exhibiting a posterior alpha rhythm. Their IQ also improved, and they were able to attend school. Early functional hemispherectomy should be considered before patients with RE are left in a serious condition due to progressive worsening of hemiplegia and seizures refractory to the available treatment.

No To Hattatsu 2011;43:373-7

研究グループ紹介

第8回鳥取大学小児神経学入門講座・第29回米子セミナー

期　日　平成22年10月2日（土）～3日（日）
会　場　鳥取大学医学部臨床講義棟（米子）
教育講演
　小児神経病理学の基礎：脳の中をのぞき見る
　伊藤雅之（国立精神・神経医療研究センター神経研究所疾研2部）
小児神経学入門講座
1. 知的障害・「発達障害」の診察
　大野耕策（鳥取大脳神経小児科）
2. 自閉症スペクトラム障害と学習障害
　―小児神経学的観点から―
　小枝達也（鳥取大地域学部地域教育学科）
3. 小児のてんかん 抗てんかん薬治療について
　平岩里佳（東部島根医療福祉センター）
4. 脳波判読の実際
　前垣義弘（鳥取大脳神経小児科）
5. よくみる小児神経疾患の画像
　藤井進也（鳥取大放射線科）
6. 小児のリハビリテーション
　北原　佶（鳥取県立総合療育センター）

グループレクチャー
1. 遺伝子診療：遺伝子診断と遺伝カウンセリング
　難波栄二（鳥取大生命機能研究支援センター遺伝子探索分野）
2. 発達障害の療育
　汐田まどか（鳥取県立総合療育センター）
3. 臨床診断に必要な神経生理検査
　前垣義弘（鳥取大脳神経小児科）
4. 筋ジストロフィーの呼吸管理と心不全治療薬の使い方
　齋田泰子（国立病院機構松江医療センター）
5. 小児神経疾患の症例呈示
　杉浦千登勢（鳥取県立総合療育センター）
米子セミナー
　症例検討会・画像検討会

次回開催予定　平成23年9月23日～24日
連絡先　鳥取大学医学部脳神経小児科（近藤章子）
　FAX：0859-38-6779
　http://www.med.tottori-u.ac.jp/dcn/

＝短　　報＝

小児発作性疾患に対する長時間ビデオ・脳波同時記録検査の有用性に関する検討

平野嘉子，小国弘量，大澤真木子

東京女子医科大学小児科

要　　旨

小児科領域では，長時間ビデオ脳波を，てんかん発作型の決定と発作性疾患の鑑別目的に施行することが多い．今回，当科で本検査を施行した患者の後方視的調査を行い，有用性についての検討を行った．対象はてんかん発作を疑い，2004年1月から2006年12月まで本検査を施行したのべ182例である．検査にて，11例（6%）は別の発作型であり，50例（27%）は非てんかん性であると証明された．また，非てんかん性のうち39例（78%）に神経・発達障害が併存していた．的確な診断は，抗てんかん薬の過剰投与防止，生活の質の向上，家族への発作指導へと発展する．以上より，長時間ビデオ脳波は発作性疾患に大変有用な検査であると確認された．

見出し語　小児，長時間ビデオ脳波，てんかん，発作性疾患鑑別，医療経済

はじめに

国際てんかん連盟（ILAE）が提唱している長時間脳波の適応は，1）てんかん症候群の診断，2）てんかん外科手術前評価，3）てんかん発作か否かの診断，4）概日周期との関連，5）睡眠との関連，6）ICUモニター，とされている[1]．さて，小児科領域では，日常診療において発作性疾患の鑑別を求められる場面に遭遇することが非常に多い．さらに，治療抵抗性で発作回数の多い難治性てんかんやてんかん性脳症の患者も少なくない．そのため，長時間ビデオ脳波は，発作性疾患の鑑別やてんかんの発作型を決定するために施行されることが多く，小児のてんかん治療において非常に有用な検査法のひとつであろうと考えられている．しかし，現在の日本において本検査は，限られた専門施設でしか行われていないのが現状であり，一般診療では，家庭用ビデオや通常脳波検査によって診断を推測せざるを得ない．小児神経外来のある一般病院で本検査が可能となれば，確実な診断と適切な治療が期待できるであろう．今回，本検査の有用性を調査するため，検査施行前後の診断をそれぞれ比較検討したので報告する．

Ⅰ　対象・方法

2004年1月から2006年12月まで長時間ビデオ脳波を施行した，のべ182例（男性84例，女性98例）について後方視的に検討を行った．いずれも問診，画像診断，通常脳波より総合して発作型診断が行われていた．多くは発作回数が日単位であり，24時間で発作の記録が可能であると判断され，長時間ビデオ脳波が施行されていた．そこで，施行前後の診断の差異について後方視的に検討した．

長時間ビデオ脳波はBio-logic社のCeegraph SEを使用した．頭皮上の電極は10-20法に基づきコロジオン固定を行い，特殊誘導や表面筋電図は必要に応じて接着した．TC＝0.1，HF＝70 Hzにて脳波を記録し，また，撮影するビデオはベッドサイドで常時患者本人が撮影されるように設置した．発作と思われる場面では，本人または介助者がマーカーボタンを押すと，ビデオ脳波上にマーキングされるよう設定した．

Ⅱ　成　　績

記録時年齢中央値は4歳9カ月（2カ月～32歳3カ月）であった．182例中139例（76%）に神経・発達障害の併存を認めた．問診と通常脳波検査で予想された発作型は，全般発作82例，部分発作52例，点頭発作25例，瞬目発作4例，微細運動発作1例，発作型未決定18例であった．長時間ビデオ脳波の結果，145例（80%）で発作時ビデオ脳波が記録され，発作診断は全般発作36例，部分発作31例，点頭発作18例，瞬目発作2例，微細発作0例，臨床発作を伴わない脳波変化8例，非てんかん性50例に変更された（図1）．84例（46%）は検査施行前の発作診断と一致していた．11例（6%）は他のてんかん発作型であることが確認され，4例は部分発作から全般発作，7例は全般発作から部分発作に変更された．当初てんかん発作と考えられていたが，検査後に非てんかん性と診断されたものは50例（27%）であった．

非てんかん性と診断された50例の検査前の診断は全般発作25例，部分発作16例，点頭発作7例，微細運動発作1例，瞬目発作1例であり，検査後に不随意運動20例，常同運動10例，心因反応9例，睡眠覚醒障害4例などに変更された（表1）．また，この50例中39

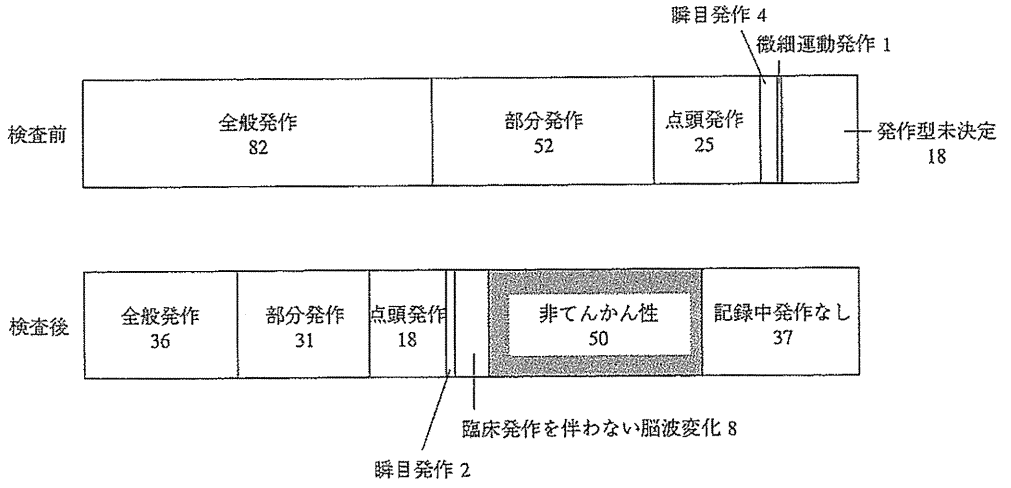

図1　長時間ビデオ脳波検査施行前後の診断名の変化

問診や通常脳波検査で予想されたてんかん発作型と一致したのは84例（46%）であった．11例は，他のてんかん発作型に変更され，また，50例は非てんかん性であった．

表1 非てんかん性であった50例の検査前後の診断名の変化

神経・発達障害併存例ののべ内訳（n=39）	検査前診断（n=50）	検査後診断（n=50）
てんかんの既往：19 （West症候群の既往：9）	全般発作：25 （ミオクロニー：13，強直：9，欠神：2，脱力：1）	不随意運動：20 （ミオクローヌス：12，ジストニア：4，交代性片麻痺：2，異常眼球運動：1，アテトーゼ：1）
精神運動発達遅滞・精神遅滞：30 （重症心身障害：10）	部分発作：16 （単純：7，複雑：9）	常同運動：10
多発奇形症候群：4	点頭発作：7	心因反応：9 （転換性障害：6，チック：3）
発達障害：2	微細運動発作：1	睡眠覚醒障害：4 （覚醒反応：2，ナルコレプシー：1，Klein-Levin症候群：1）
不随意運動：2	瞬目発作：1	反射：4 （驚愕：2，失神：1，啼泣後無呼吸：1）
		体幹筋力低下：2
		偏頭痛：1

注：多くは神経・発達障害が併存していた．

例（78%）に神経・発達障害の併存を認めた．のべ内訳は，てんかんあるいはてんかんの既往19例（9例はWest症候群の既往），精神運動発達遅滞・精神遅滞30例（うち重症心身障害10例），多発奇形症候群4例などであり，また，成因として周産期異常を18例に認めた．

Ⅲ 考 察

小児科領域では，熱性けいれんや失神を含め発作性疾患を診察する機会が非常に多い．また，小児てんかんは，小児の神経疾患の中でも特に頻度が高く，確実な診断と適切な治療を求められる．しかし，医療者が実際に発作を目撃することは稀である．欧米では，発作性疾患の鑑別や発作型の同定のため，積極的に長時間ビデオ脳波検査を導入している．Asanoらは，小児患者1,000名に長時間ビデオ脳波検査を行ったところ，約半数はILAEてんかん症候群分類が可能なてんかんであったと報告した[2]．Salinskyらは通常脳波を繰り返し施行すること[3]，Veldhuizenらは断眠などの負荷を行うこと[4]で，異常波の検出率が上がると述べているが，McGonigalらはビデオ脳波の有用性に着目し[5]，さらにAlvingらが短時間ビデオ脳波に比べ，長時間ビデオ脳波では，発作時の記録や発作間欠期の脳波異常の検出率を上昇させると報告した[6]．Ghougassianらは平均5.6日モニタリングした結果，30%は発作性イベントを認めなかったが，18%は通常脳波で検出し得なかった新たなてんかん性異常を検出することに成功したと報告した[7]．また，Mohanらは，たとえ1日であっても長時間ビデオ脳波を施行することは，発作性イベントがなくとも何らかの異常運動症状をとらえることができ，意義があると考えている[8]．今回の研究でも，46%は問診などで予測された発作型に一致していたが，6%は異なった別の発作型であることがわかり，今までの報告とほぼ一致した結果となった．

さて，小児期においてんかん発作と鑑別を要する代表的な発作性疾患は，失神発作，息止め発作，夜驚症，心因反応，低血糖発作などである．また，脳性麻痺や自閉症などをもつ患者の不随意運動や習慣性行動は，ときにてんかん発作との鑑別が困難である．問診，家庭用ビデオ記録，通常脳波にて一部は鑑別可能であるが，それらの手段を用いてもてんかん性か否かの判断に苦慮することは少なくない．さらに，発作性イベントが心因性や心因反応により二次的に生じると，より鑑別困難となる．Martinらは，てんかんと診断されていた患者に長時間ビデオ脳波を施行したところ，32.3%に偽発作を認め，また，そのうち5.3%は実際のてんかん発作も合併していたと報告し[9]，Leeらは検討症例の20%は非てんかん性であったと報告している[10]．実際，我々の研究でも50例（27%）は非てんかん性であり，既知の報告とほぼ一致していると考えられた．このように，神経・発達障害を合併する患者では，比較的高率に非てんかん性発作がみられることから，治療抵抗性の頻回発作を有する場合は非てんかん性の可能性に十分注意する必要があると考えられた．以上より，日常診療において現在行われている，限られた手法のみでてんかん発作か否かの判断をすることには限界があり，確定診断に苦慮するような発作が日単位である場合は，長時間ビデオ脳波を用いることが非常に有用であると推察された．

一方，いかなる検査においても，施行の際には患者や医療者に対する制約や問題が少なからず存在する．長時間ビデオ脳波施行時の患者側の制約・問題点は，1～2日間短期入院しなければならないこと，記録中は定められた範囲以内で生活しなければならないこと，また，自身が発作マーカーボタンを押せない場合は介助者が付き添い常時発作を観察する必要があることなどである．しかし，Martinらは，発作性疾患が非てんかん性であると正しく診断をすることは外来受診日数，受診料，投薬料，検査費用，救急外来受診回数，受診料の減少につながり，結果として患者の生活の質向上だけでなく，医療費削減にも非常に重要であると言及している[11]．さらに，Chemmanamらが，てんかん患者にかかる直接的な費用は，抗てんかん薬治療費，診断に必要な検査費，病院受診料であり，毎年一定の医療費が生じるため，不必要な医療費を発生させないためにも適切な問診，検査，治療が必要であると提唱している[12]．このように，患者の生活の質だけでなく，医療費の面からも，長時間ビデオ脳波検査にて的確な診断を行うことは，入院という制約，検査費用という問題を上回る有益な検査であると考えられた．

医療者側の問題としては，高い専門性が要求されることである．当科で長時間ビデオ脳波検査を施行する場合，通常はコロジオンを用いた特殊な方法で脳波を装着するため，検査に協力的な患者であっても，装着には最低30分必要である．また，小児の場合は装着にあたり，検査技師だけでなく，最低2人以上の医師が必要である．装着後は，各自の病室で記録するが，検査補助員と医師で脳波計やビデオを的確な位置に設置し，患者家族に行動範囲や発作時の記録法などを説明することに1時間以上を要する．記録時は，発作だけでなく脳波計やビデオの状態を確認するため，夜間も看護師や担当医

が定期的に巡回しなければならない．記録終了後，記録した24時間または48時間分の脳波は，脳波専門医を中心としたてんかんチームにより詳細に解析される．このように長時間ビデオ・脳波検査では多くの時間と労力が必要なことも事実である．Chemmanamらは，医療機関側に必要なものは，長時間ビデオ脳波モニタリング機器，長時間脳波に精通した臨床検査技師，発作ケアに精通した看護スタッフ，脳波判読の技術のある医師とてんかん専門医である，と述べている[12]．大変有用な検査であるが，一方で高い専門性が要求される検査であることは明確である．

今年より長時間脳波は保険適応となったが，1日700点で最長5日までである上，てんかん外科手術前後のみに限られており，発作鑑別のために施行した場合は対象にはならない．本検査は，発作性疾患を扱う医療機関に普及すべきであると考えられるが，その得られる利点や経済性を考慮した保険適応の必要性が望まれる．

文　献

1) Commission on Classification and Terminology of the International League against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989;**30**:389-99.
2) Asano E, Pawlak C, Shah A, et al. The diagnostic value of initial video-EEG monitoring in children — review of 1000 cases. *Epilepsy Res* 2005;**66**:129-35.
3) Salinsky M, Kanter R, Dasheiff RM. Effectiveness of multiple EEGs in supporting the diagnosis of epilepsy: an operational curve. *Epilepsia* 1987;**28**:331-4.
4) Veldhuizen R, Binnie CD, Beintema DJ. The effect of sleep deprivation on the EEG in epilepsy. *Electroencephalogr Clin Neurophysiol* 1983;**55**:505-12.
5) McGonigal A, Russell AJ, Mallik AK, Oto M, Duncan R. Use of short term video EEG in the diagnosis of attack disorders. *J Neurol Neurosurg Psychiatry* 2004;**75**:771-2.
6) Alving J, Beniczky S. Diagnostic usefulness and duration of the inpatient long-term video-EEG monitoring: findings in patients extensively investigated before the monitoring. *Seizure* 2009;**18**:470-3.
7) Ghougassian DF, d'Souza W, Cook MJ, O'Brien TJ. Evaluating the utility of inpatient video-EEG monitoring. *Epilepsia* 2004;**45**:928-32.
8) Mohan KK, Markand ON, Salanova V. Diagnostic utility of video EEG monitoring in paroxysmal events. *Acta Neurol Scand* 1996;**94**:320-5.
9) Martin R, Burneo JG, Prasad A, et al. Frequency of epilepsy in patients with psychogenic seizures monitored by video-EEG. *Neurology* 2003;**61**:1791-2.
10) Lee YY, Lee MY, Chen IA, et al. Long-term video-EEG monitoring for paroxysmal events. *Chang Gung Med J* 2009;**32**:305-12.
11) Martin RC, Gilliam FG, Kilgore M, Faught E, Kuzniecky R. Improved health care resource utilization following video-EEG-confirmed diagnosis of nonepileptic psychogenic seizures. *Seizure* 1998;**7**:385-90.
12) Chemmanam T, Radhakrishnan A, Sarma SP, Radhakrishnan K. A prospective study on the cost-effective utilization of long-term inpatient video-EEG monitoring in a developing country. *J Clin Neurophysiol* 2009;**26**:123-8.

連絡先　〒162-8666　東京都新宿区河田町8-1
東京女子医科大学小児科（平野嘉子）
E-mail: yochi(a)ped.twmu.ac.jp
（受付日：2010. 8. 23，受理日：2010. 12. 28）

Epilepsia, 52(6):1144–1149, 2011
doi: 10.1111/j.1528-1167.2011.03053.x

FULL-LENGTH ORIGINAL RESEARCH

Retrospective multiinstitutional study of the prevalence of early death in Dravet syndrome

*[1]Masako Sakauchi, *[1]Hirokazu Oguni, *Ikuko Kato, *[1]Makiko Osawa, †[1]Shinichi Hirose, ‡Sunao Kaneko, §[1]Yukitoshi Takahashi, §Rumiko Takayama, and §Tateki Fujiwara

*Department of Pediatrics, Tokyo Women's Medical University, Tokyo, Japan; †Department of Pediatrics, School of Medicine, Fukuoka University, Fukuoka, Japan; ‡Department of Neuropsychiatry, School of Medicine, Hirosaki University, Aomori, Japan; and §National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorder, Shizuoka, Japan

Summary

Purpose: A questionnaire survey was conducted in Japan to investigate the causes and prevalence of death related to Dravet syndrome.

Methods: A questionnaire was delivered to 246 hospitals at which physicians were treating childhood epilepsy to gain information about the total number of patients with Dravet syndrome and their prevalence of early death.

Key Findings: Responses to the survey were collected from 91 hospitals, and a total of 63 of 623 patients with Dravet syndrome died. Data from 59 of these patients were analyzed. The patients' ages at death ranged from 13 months to 24 years and 11 months, with a median age of 6 years and 8 months. The analysis showed that the risk of mortality remained high up to approximately 12 years of age. The causes of mortality included sudden death in 31 patients (53%), acute encephalopathy with status epilepticus (SE) in 21 patients (36%), drowning in 6 patients (10%), and acute hepatopathy in one patient (1%). The incidence of sudden death reached a first peak at 1–3 years of age and reached a second peak at 18 years and older. In contrast, the incidence of acute encephalopathy with SE reached a sharp peak at 6 years of age. Seven of 10 patients who underwent an *SCN1A* mutation analysis exhibited positive mutations without a specific mutation site.

Significance: In the present study, the prevalence of Dravet syndrome–related mortality was 10.1%. The incidence of sudden death and acute encephalopathy with SE was the highest in infancy (1–3 years) and at early school ages (with a peak at 6 years), respectively. After approximately 12 years of age, the risk of mortality declined sharply. Neither the treatment nor the number of seizures was associated with any cause of mortality. In addition, it is difficult to predict which factors lead to a fatal outcome.

KEY WORDS: Dravet syndrome, Severe myoclonic epilepsy in infants, Mortality, Sudden death, Acute encephalopathy.

Dravet syndrome is one of the most malignant epileptic syndromes among the various types of childhood epilepsy (Oguni et al., 2001; Dravet et al., 2005). Recent advances in molecular biology have demonstrated that *SCN1A* mutations cause this rare but catastrophic epilepsy and have increased our understanding of its pathogenesis (Claes et al., 2001). This disorder exhibits specific clinical features: Seizures are easily provoked by a rise in the body temperature; various types of seizures are combined with one another; and strong photosensitivities and pattern sensitivities are involved. Furthermore, sudden death from unknown causes and mortality or serious sequelae associated with lethal status epilepticus (SE) have been reported, accounting for a percentage that is constant from author to author (Oguni et al., 2001; Dravet et al., 2005). The number of patients diagnosed with Dravet syndrome has increased throughout the world (Dravet et al., 2005); the *SCN1A* mutation test facilitates a definitive diagnosis in the early stage of the condition, and characteristic clinical features have been widely recognized among pediatric neurologists. In contrast, the seizures and mental prognosis do not seem to improve despite various treatment trials that have been conducted. In addition, unexpected death during the treatment course for this catastrophic disorder may have influenced the reliance of patients' families on physicians (So et al., 2009). Until now, no systematic study has been conducted to clarify the incidence of unexpected death or the prognostic factors associated with this mortality. Because Dravet syndrome is a rare type of epileptic syndrome, an analysis involving a number of patients in a single hospital is difficult, necessitating a nationwide survey. In this study, we conducted a nationwide questionnaire survey regarding Dravet syndrome–related mortality in Japan and investigated the

Accepted February 2, 2011; Early View publication April 11, 2011.
Address correspondence to Hirokazu Oguni, Department of Pediatrics, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162, Japan. E-mail: hoguni@ped.twmu.ac.jp
[1]Dravet Syndrome Prognosis Research Group (see Appendix).

causes of mortality, the clinical characteristics at the time of death, and the risk factors related to mortality. The results may help provide information that prevents mortality for the families of children with this disorder and for health care professionals.

Methods

In July 2009, a questionnaire was delivered to the epilepsy training hospitals that were authorized by the Japanese Society of Epilepsy, to hospitals/institutions that were authorized to train specialists from the Society of Pediatric Neurology, and to university hospitals (total: 246 hospitals). This survey allowed us to collect information about the total number of past and present patients with Dravet syndrome, the number of patients who died, and the number of patients with serious sequelae. A secondary questionnaire was sent by mail to the 26 hospitals that reported mortality cases to obtain information on the following items for each patient: (1) gender; (2) age at the onset of epilepsy (in months); (3) clinical type (typical or borderline groups) (Fujiwara et al., 2003; Oguni et al., 2005); (4) presence or absence of an *SCN1A* gene test and its results; (5) age at death; (6) Causes of mortality; (7) presence or absence of risk factors at death, such as fever/infection, bathing, seizures, and the child's state (sleep or awake); (8) frequency of seizures and of SE before death; (9) treatment regimen; (10) neurological condition; (11) electroencephalographic and neuroimaging findings; and (12) autopsy findings.

The time from the onset of epilepsy to death and the age at death were very close because of the early onset of the epilepsy; therefore, we compared the age at death between the typical and borderline groups and among the causes of death.

Prior to this study, the protocol was approved by the Tokyo Women's Medical University Ethics Review Board and by the Dravet Syndrome Prognosis Survey/Study Group Ethics Review Board.

Statistical analyses

Statistical analyses were performed using SPSS 15.0J (SPSS Japan, Tokyo, Japan) for Windows. The chi-square test, *t*-test, and Mann-Whitney *U*-test were employed to compare the results between two variables. A comparison among more than three variables was performed using the chi-square test with cross tabulation. The Bonferroni correction was added to the statistics when multiple statistical comparisons were performed between several groups. A p-value of <0.05 was regarded as significant.

Results

Subjects

Responses were collected from 147 of the 246 hospitals (response rate: 59.8%). In 91 of the 147 hospitals, a total of 623 patients with Dravet syndrome were treated (median: two patients/hospital; range 1–109/hospital). In addition, data on 63 patients who died were collected from 26 hospitals (438 patients). Of these patients, the data from 59, excluding 4 for whom the information at the time of death was insufficient, were analyzed.

Clinical characteristics of the patients who died

In the 59 patients included in the analyses, the male-to-female ratio was 26:33. The ages of the patients at the onset of epilepsy ranged from 2–10 months, with a mean of 5.1 months. Of the 59 patients included in the analyses, 20 patients comprised the borderline group without myoclonic or atypical absence seizures, and 39 patients comprised the typical group (Table 1). No significant differences were observed between the two groups for the age at the onset of epilepsy, the age at death, the causes of mortality, the frequency of seizures before death, or the number of antiepileptic drugs ($p > 0.05$). In the typical group, the frequency of seizures before death was slightly higher than that in the borderline group, and the rates of mental retardation were slightly higher; however, there were no significant differences in the rates of severe mental retardation between the two groups ($p > 0.05$). The number of antiepileptic drugs, the frequency of seizures, and the grade of mental retardation were unclear or not described for three patients, three patients, and one patient, respectively.

Mortality

For the 26 hospitals that reported at least one patient who died for this nationwide survey, mortality accounted for 14.4% of their patients with Dravet syndrome (63 of 438 patients). When using the 91 hospitals (623 patients) as a denominator population, the prevalence of death was 10.1%.

Causes of mortality and age distribution

The patients' ages at the time of death ranged from 13 months to 24 years and 11 months, with a median age of 6 years and 8 months. The ages were distributed most frequently between 13 months and approximately 12 years and were rarely older in both the typical and borderline groups (Fig. 1). The distribution of the time between the two groups did not differ significantly ($p = 2.88 > 0.05$).

The causes of mortality were largely classified into three groups: sudden death (n = 31, 53%), acute encephalopathy with SE (n = 21, 36%), and drowning (n = 6, 10%). The remaining one patient died of fulminant hepatitis B (1%). When reviewing the age distribution with respect to the causes of mortality, two characteristic patterns were observed (Fig. 2). Briefly, the prevalence of sudden death reached a first peak at 1–3 years of age and a second small peak at 18 years and older. In contrast, the prevalence of acute encephalopathy with SE was prevalent between

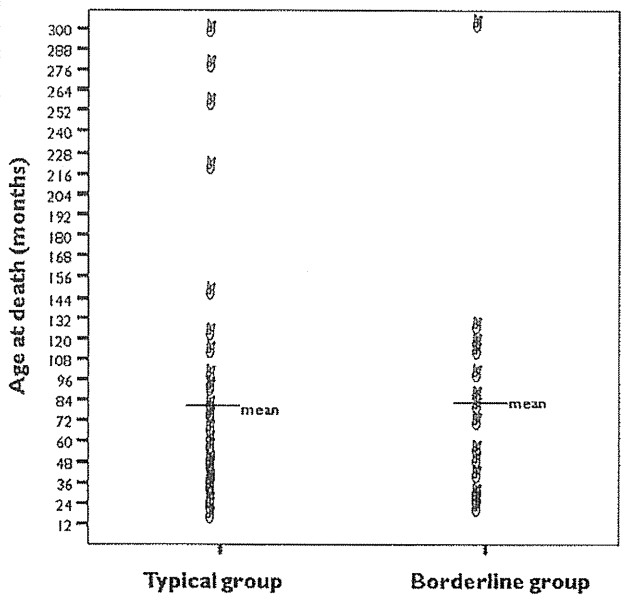

Figure 1.
Dot plots showing the distribution of age at death in the typical and borderline groups (n = 59). The age at death appeared prevalent between 13 and 140 months of age and sparse thereafter in both typical and borderline groups. No significant difference was observed between these two groups ($p > 0.05$).
Epilepsia © ILAE

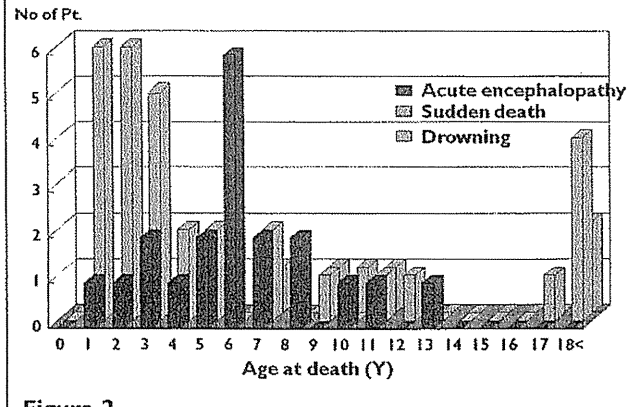

Figure 2.
Distribution of ages at death with respect to the causes of mortality. The incidence of sudden death reached a first peak at 1–3 years old and a second small peak at 18 years and older. In contrast, the acute encephalopathy-related mortality rate reached a sharp peak at 6 years old. All patients were 7 years old or older in the drowning group.
Epilepsia © ILAE

approximately 3 and 8 years of age with a sharp peak at age 6.

Causes of mortality and clinical features

The causes of mortality were associated with fever and the age at death (Table 2). In the sudden death group, the median age at death was 43 months, which was lower than that (72 months) in the acute encephalopathy group. These two groups exhibited characteristic age distributions with different peaks ($p < 0.05$), that is, the sudden death group was more likely to die at an age <47 months and after 168 months, whereas the acute encephalopathy group was more likely to experience death between 48 and 167 months (Table 2). In 81% of the patients who died of acute encephalopathy with SE, fever was noted at the time of death. In addition, fever was observed in 26% of the patients who died suddenly ($p < 0.05$). Twenty (65%) and eight (26%) of the 31 patients in the sudden death group were found to have died during sleep (or in the early morning) and during the daytime, respectively. For the remaining three patients, information about the exact time at their deaths was not available.

In 6 of the 31 patients in the sudden death group, rigid limbs and trace amounts of vomit suggested that epileptic seizures or suffocation was involved in their deaths. However, an autopsy was not performed for any of these six patients who showed the rigid limbs and trace amounts of vomit; therefore, the cause of death was not specified. In 14 patients (67%) in the acute encephalopathy group, systemic involvements, such as multiple organ failure and disseminated intravascular coagulation (DIC), became evident during or after the successful treatment of SE. Therefore, the clinical response and features of SE differed from those that the children had repeatedly experienced before. This lethal febrile SE developed suddenly at a peak age of 6 years, when the seizure or SE frequency was abated, and led to coma and multiple organ failure despite vigorous treatment. The interval of time from the onset of SE until death was 24 h or less in five patients (24%), 1 week or less in six patients (29%), more than 1 week in six patients (29%), and not known for the remaining four patients (18%).

An autopsy was performed for only 6 (10%) of the 59 patients: one who died suddenly, 4 who died of acute encephalopathy with SE, and one who died of fulminant hepatitis B. For these six patients, the causes of mortality were identified as Reye syndrome for two patients and fulminant hepatitis for one patient. However, for the remaining three patients, no cause of mortality was identified, despite the autopsy.

In the six patients who died from drowning, accidents occurred while bathing at home or in the hospital. All patients were 7 years old or older, including two patients older than 18 years of age; as a result, these patients were permitted to bathe alone.

SCN1A mutation analysis

An *SCN1A* gene test was performed for only 10 of the 59 patients. Gene mutations were detected for 7 of these 10 patients. The mutation sites were scattered in the *SCN1A* gene tests that were previously reported; as a result, no

Table 1. Clinical manifestations and phenotype

	Typical (N = 39)	Borderline (N = 20)	All cases (N = 59)	p-Value*
Gender (M/F)	17/22	9/11	26/33	3.99
Age at onset (mo.)	4.9 ± 1.7	5.5 ± 2.0	5.1 ± 1.8	2.04
Age at death (mo.)	80.7 ± 73.1	79.5 ± 70.5	80.4 ± 71.6	2.88
Cause of death Sudden/status/drowning	21/15/3	10/6/3	31/21/6	2.80
Seizure frequency Daily/weekly/monthly	13/16/8	2/7/10	15/23/18	0.567
Number of AED polytherapy (<4)/2–3	15/21	6/12	23/33	4.788
Mental retardation Severe/moderate/mild	18/14/6	4/9/7	22/23/13	0.980

M, male; F, female, mo., months; AEDs, antiepileptic drugs.
*The Bonferroni collection was added to p-values.

Table 2. Comparison between those with sudden death and acute encephalopathy

	Sudden death (N = 31)	Acute encephalopathy (N = 21)	p-Value*
Gender (M/F)	18/13	5/16	0.42
Phenotype (typical/borderline)	21/10	15/6	8.0
Age at death (mo.) ≤47 or ≤168/48–167	22/9	5/16	0.01*
Fever at death (%)	25.8	81.0	0.00*
Seizure frequency Daily/weekly/monthly	8/11/7	7/5/9	3.69
Mental retardation Severe/moderate/mild	12/10/9	7/9/4	2.16
AED polytherapy <4 (%)	32.3	38.1	4.86
Epileptic EEG abnormality (%)	56.7	42.1	4.50
Neuroimaging abnormality (%)	29.0	33.3	5.13

M, male; F, female, mo., months; AED, antiepileptic drug.
*The Bonferroni collection was added to p values.

mutation site that was characteristic of mortality was detected (Depienne et al., 2009; Lossin, 2009).

Discussion

In this nationwide survey, data were collected for 63 patients with Dravet syndrome who died, and data from 59 of these patients were used for the analyses. The result showed that the risk of mortality remained high up to the age of approximately 12 years of age, regardless of the clinical type, and sharply declined thereafter. The causes of mortality were classified into three types: sudden death, acute encephalopathy with SE, and accidents (mostly drowning). In particular, sudden death and acute encephalopathy with SE accounted for 53% and 31% of the causes of death, respectively.

The incidence of sudden death reached a first peak at 1–3 years of age and reached a second small peak at 18 years and older. Sudden unexpected death in epilepsy (SUDEP) has been reported to account for approximately 2–18% of all epilepsy-related deaths. Therefore, the incidence of SUDEP in this disorder is high (Gaitatzis & Sander, 2004; Tomson et al., 2008). During infancy, patients with Dravet syndrome experience recurrent febrile/afebrile SE despite vigorous antiepileptic drug (AED) treatments (Claes et al., 2001; Dravet et al., 2005). In the present study, neither the number of AEDs nor the frequency of the seizures was abnormally high immediately before death; however, no control group was established. The epileptic seizures associated with Dravet syndrome are presumably generated by epileptogenic pyramidal neurons because of an *SCN1A* mutation–mediated dysfunction of inhibitory interneurons (Yu et al., 2006; Ogiwara et al., 2007). The involvement of this channelopathy in epilepsy suggests that cardiac arrhythmia is a complication that is involved in the episodes of sudden death. Both arrhythmia and respiratory hypoventilation have been considered to be causes of SUDEP (Gaitatzis & Sander, 2004; Tomson et al., 2008). Most patients with Dravet syndrome who died suddenly were found in bed early in the morning or after sleeping in the afternoon. This result is consistent with common-type SUDEP. Neither electrocardiographic abnormalities nor heart/respiratory dysfunction has been reported in any children with this disorder. Unfortunately, no study has demonstrated any other arrhythmia-associated gene mutations in patients with Dravet syndrome. More work is needed to clarify whether the *SCN1A* mutation site is associated with sudden death in Dravet syndrome.

The mortality rate resulting from acute encephalopathy with SE reached a sharp peak at 6 years old (prevalent between 4 and 8 years of age). In these cases, coma or multiple organ failure led to a fatal outcome despite seizure control. Recently, catastrophic SE that led to severe neurologic sequelae has been reported in infants with Dravet syndrome (Chipaux et al., 2010; Takayanagi et al., 2010). The catastrophic SE did not seem to be related to a delay in seizure treatment or to insufficient treatment. This SE was always associated with fever and was resistant to conventional SE

treatment, requiring high doses of barbiturates or short-acting barbiturates to control the SE, which may have contributed to cerebral damage resulting from a reduction of cerebral blood flow (Chipaux et al., 2010). Although barbiturates are often chosen to treat refractory SE in the intensive care unit (ICU) setting, it may be beneficial to consider an alternative treatment such as propofol or a combination of hypothermia therapies in these cases (Munakata et al., 2000). The frequency of SE or of prolonged seizures decreases markedly in children with Dravet syndrome who are older than 4 years of age. Therefore, mortality related to acute encephalopathy with SE at this age was an unexpected event for the families of these patients and for the health care professionals (Oguni et al., 2001; Dravet et al., 2005). In Japan, fulminant acute encephalopathy associated with SE in children has recently been identified as a complication of an influenza infection. The individual genetic factors that contribute to the susceptibility to acute encephalopathy may suggest an important role in its pathogenesis (Mizuguchi et al., 2007). For patients with Dravet syndrome, *SCN1A* mutations are related to seizures that are markedly sensitive to elevated temperature. In an *SCN1A*-knockout mouse model, a rise in body temperature markedly decreased the threshold of the seizures; therefore, the complication of acute encephalopathy with SE may be associated with *SCN1A* mutations (Oakley et al., 2009). A previous study indicated that Dravet syndrome was present in most patients who had been diagnosed with vaccine encephalopathy (Berkovic et al., 2006). This disorder frequently causes acute encephalopathy; however, the peak incidence of fatal acute encephalopathy with SE at approximately 6 years of age should be clarified.

All of the patients who had accidental deaths drowned while bathing. Drowning-related mortality is avoidable in patients with Dravet syndrome and in patients with other types of epilepsy (Gaitatzis & Sander, 2004). Because seizures that are hypersensitive to elevated body temperature continue through adulthood in most patients with this disorder, the Japanese-style bathing that raises body temperature is a potential risk factor (Oguni et al., 2001). Therefore, it is necessary to train caregivers to be vigilant when the patients take a bath.

The prevalence of mortality in patients with Dravet syndrome has been shown to range from 5–20%, which is markedly higher than in patients with other types of epilepsy (Oguni et al., 2001; Dravet et al., 2005). In the present study, the statistical analyses involving the 91 hospitals showed a mortality rate of 10.1%. The data from the 26 hospitals that reported mortality cases indicated that the mortality rate was 14.4%. However, a limitation of this study was that the survey period differed among the hospitals, leading to difficulty in accurately evaluating the population (as a denominator). In addition, the lack of detailed information on the population did not permit us to create a survival curve. Other limitations of this study included a 60% response rate to the questionnaire, retrospective case ascertainment, a very low autopsy rate, and a low incidence of *SCN1A* mutation analyses, all of which lowered the validity of this study. However, even if these limitations are considered, the prevalence of early death would be estimated to be 10–15%, which is still markedly higher than the rate in patients with other types of epilepsies.

The mortality rate in childhood epilepsy has been estimated to be 3–7 times higher than that in the general population (Berg et al., 2004; Autry et al., 2010). The risk factors for mortality were considered to be symptomatic etiology, epileptic encephalopathy, especially West and Lennox-Gastaut syndromes, and severe comorbid neurologic disorders. The death rate for the epileptic syndromes was highest for symptomatic generalized epilepsy, which was 15–16% and was almost equivalent to that of Dravet syndrome. However, the causes of death for generalized epilepsy were markedly different from those for Dravet syndrome and were mostly related to the complications of severe neurologic deficits (infections and accidents, among others), not to the occurrences of seizures or sudden death.

In conclusion, this study identifies the high-risk age periods with respect to the specific causes of mortality; however, no other prognostic factors, including *SCN1A* mutations, could be discerned. Since the 1980s, there has been a strong medical/social interest in SUDEP in patients with patients (Nilsson et al., 1999; Gaitatzis & Sander, 2004; Tomson et al., 2008). According to a report that was published by a collaborative special committee of the American Society of Epilepsy and the Foundation of Epilepsy, future endeavors should emphasize the importance of talking with patients' families about SUDEP, facilitating physicians' and community members' understanding of SUDEP, and planning nationwide/international prospective studies (So et al., 2009). It is necessary to provide the information obtained in this nationwide survey regarding the causes of mortality and the high-risk age periods to the hospitals that are involved in the treatment of this disorder and to the patients' families, despite objections that have been raised concerning the difficulty of SUDEP prediction and families' anxiety levels. A worldwide multiinstitutional study needs to be performed to identify the risk factors at a molecular level and to prevent catastrophic events associated with this syndrome.

Acknowledgments

We are grateful to all of the doctors who participated in this nationwide study and who provided clinical data on the patients. This study was funded in part by Research Grants (21210301) for the Specified Disease Treatment Research Program from the Ministry of Health, Labor, and Welfare.

Disclosure

There are no conflicts of interest related to this manuscript. We confirm that we have read the Journal's position regarding issues pertaining to ethical publication and affirm that this report is consistent with those guidelines.

References

Autry AR, Trevathan E, Van Naarden Braun K, Yeargin-Allsopp M. (2010) Increased risk of death among children with Lennox-Gastaut syndrome and infantile spasms. *J Child Neurol* 25:441–447.

Berg AT, Shinnar S, Testa FM, Levy SR, Smith SN, Beckerman B. (2004) Mortality in childhood-onset epilepsy. *Arch Pediatr Adolesc Med* 158:1147–1152.

Berkovic SF, Harkin L, McMahon JM, Pelekanos JT, Zuberi SM, Wirrell EC, Gill DS, Iona X, Mulley JC, Scheffer IE. (2006) De-novo mutations of the sodium channel gene *SCN1A* in alleged vaccine encephalopathy: a retrospective study. *Lancet Neurol* 5:488–492.

Chipaux M, Villeneuve N, Sabouraud P, Desguerre I, Boddaert N, Depienne C, Chiron C, Dulac O, Nabbout R. (2010) Unusual consequences of status epilepticus in Dravet syndrome. *Seizure* 19:190–194.

Claes L, Del-Favero J, Ceulemans B, Lagae L, Van Broeckhoven C, De Jonghe P. (2001) De novo mutations in the sodium-channel gene *SCN1A* cause severe myoclonic epilepsy of infancy. *Am J Hum Genet* 68:1327–1332.

Depienne C, Trouillard O, Saint-Martin C, Gourfinkel-An I, Bouteiller D, Carpentier W, Keren B, Abert B, Gautier A, Baulac S, Arzimanoglou A, Cazeneuve C, Nabbout R, LeGuern E. (2009) Spectrum of *SCN1A* gene mutations associated with Dravet syndrome: analysis of 333 patients. *J Med Genet* 46:183–191.

Dravet C, Bureau M, Oguni H, Fukuyama Y, Cokar O. (2005) Severe myoclonic epilepsy in infancy (Dravet syndrome). In Roger J, Bureau M, Dravet C, Genton P, Tassinari CA, Wolf P (Eds) *Epileptic syndromes in infancy, childhood and adolescence*, 4th ed. John Libbey Eurotext Ltd, London and Paris, pp. 89–113.

Fujiwara T, Sugawara T, Mazaki-Miyazaki E, Takahashi Y, Fukushima K, Watanabe M, Hara K, Morikawa T, Yagi K, Yamakawa K, Inoue Y. (2003) Mutations of sodium channel α subunit type 1 (*SCN1A*) in intractable childhood epilepsies with frequent generalized tonic clonic seizures. *Brain* 126:531–546.

Gaitatzis A, Sander JW. (2004) The mortality of epilepsy revisited. *Epileptic Disord* 6:3–13.

Lossin C. (2009) A catalog of *SCN1A* variants. *Brain Dev* 31:114–130.

Mizuguchi M, Yamanouchi H, Ichiyama T, Shiomi M. (2007) Acute encephalopathy associated with influenza and other viral infections. *Acta Neurol Scand Suppl* 186:45–56.

Munakata M, Kato R, Yokoyama H, Haginoya K, Tanaka Y, Kayaba J, Kato T, Takayanagi R, Endo H, Hasegawa R, Ejima Y, Hoshi K, Iinuma K. (2000) Combined therapy with hypothermia and anticytokine agents in influenza A encephalopathy. *Brain Dev* 22:373–377.

Nilsson L, Farahmand BY, Persson PG, Thiblin I, Tomson T. (1999) Risk factors for sudden unexpected death in epilepsy: a case–control study. *Lancet* 353:888–893.

Oakley JC, Kalume F, Yu FH, Scheuer T, Catterall WA. (2009) Temperature- and age-dependent seizures in a mouse model of severe myoclonic epilepsy in infancy. *Proc Natl Acad Sci U S A* 106:3994–3999.

Ogiwara I, Miyamoto H, Morita N, Atapour N, Mazaki E, Inoue I, Takeuchi T, Itohara S, Yanagawa Y, Obata K, Furuichi T, Hensch TK, Yamakawa K. (2007) Na(v)1.1 localizes to axons of parvalbumin-positive inhibitory interneurons: a circuit basis for epileptic seizures in mice carrying an *Scn1a* gene mutation. *J Neurosci* 27:5903–5914.

Oguni H, Hayashi K, Awaya Y, Fukuyama Y, Osawa M. (2001) Severe myoclonic epilepsy in infants – a review based on the Tokyo Women's Medical University series of 84 cases. *Brain Dev* 23:736–748.

Oguni H, Hayashi K, Osawa M, Awaya Y, Fukuyama Y, Fukuma G, Hirose S, Mitsudome A, Kaneko S. (2005) Severe myoclonic epilepsy in infants. Typical and borderline groups in relation to *SCN1A* mutations. In Delgado-Escueta V, Guerrini R, Medina MT, Genton P, Bureau M, Dravet C (Eds) *Advances in neurology, vol. 95, myoclonic epilepsies*. Lippincott Williams & Wilkins, Philadelphia, pp. 103–117.

So EL, Bainbridge J, Buchhalter JR, Donalty J, Donner EJ, Finucane A, Graves NM, Hirsch LJ, Montouris GD, Temkin NR, Wiebe S, Sierzant TL. (2009) Report of the American Epilepsy Society and the Epilepsy Foundation Joint Task Force on Sudden Unexpected Death in Epilepsy. *Epilepsia* 50:917–922.

Takayanagi M, Haginoya K, Umehara N, Kitamura T, Numata Y, Wakusawa K, Hino-Fukuyo N, Mazaki E, Yamakawa K, Ohura T, Ohtake M. (2010) Acute encephalopathy with a truncation mutation in the *SCN1A* gene: a case report. *Epilepsia* 51:1886–1888.

Tomson T, Nashef L, Ryvlin P. (2008) Sudden unexpected death in epilepsy: current knowledge and future directions. *Lancet Neurol* 7:1021–1031.

Yu FH, Mantegazza M, Westenbroek RE, Robbins CA, Kalume F, Burton KA, Spain WJ, McKnight GS, Scheuer T, Catterall WA. (2006) Reduced sodium current in GABAergic interneurons in a mouse model of severe myoclonic epilepsy in infancy. *Nat Neurosci* 9:1142–1149.

Appendix

The Dravet Syndrome Prognosis Research Group included the following pediatric neurologists who contributed to this study: Hideo Aiba (Shizuoka Children's Hospital), Akashi Ishikawa (Nirenokai Children's Clinic), Yuji Inaba (Shinshu University Hospital), George Imataka (Dokkyo Medical University), Shoichi Endo (Kagawa Children's Hospital), Iori Ohmori (Okayama University), Kyou Kajitani (Kawasaki Hospital), Osamu Kanazawa (Saitama Medical University Hospital), Hisashi Kawawaki (Osaka City Medical Center), Toru Konishi (Nagaoka Rehabilitation Center for Disabled Children), Nobuzo Shimizu (Gunma Institute for Children with Physical Disabilities), Takashi Soga (Epilepsy Center Bethel), Tomoyuki Takano (Shiga University of Medical Science Hospital), Jun Toyama (Nishi-Niigata Chuo National Hospital), Shinichiro Hamano (Saitama Children's Medical Center), Tatsuya Fukasawa (Nagoya University Hospital), Katsuyuki Fukushima (Fukushima Neuro Clinic), Mitsunari Fukuda (Ehime University Hospital), Naomi Fukuyo (Tohoku University Hospital), Hirofumi Fujita (Hirosaki University School of Medicine & Hospital), Shinji Fujimoto (Tsutsujigaoka Children's Clinic), Kimio Minagawa (Hokkaido Medical Center for Child Health and Rehabilitation), Susumu Miyake (Kagawa Prefectural Central Hospital), Nobuko Moriyama (Ibaraki Children's Hospital), and Keiichi Yamamoto (Isehara Kyodo Hospital).

ELSEVIER

Brain & Development 33 (2011) 207–212

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Review article

Treatment of benign focal epilepsies in children: When and how should be treated?

Hirokazu Oguni *

Department of Pediatrics, Tokyo Women's Medical University, Tokyo, Japan

Abstract

Benign focal epilepsies represent almost one-fourth of all childhood epilepsies and are a frequent occurrence in clinical practice. They include benign infantile seizures (BIS), Panayiotopoulos syndrome (PS), and benign childhood epilepsy with centrotemporal spikes (BCECTS) in this order of the onset age. Because the prognosis is always excellent in patients with benign focal epilepsies, we must consider the risks and benefits of chronic antiepileptic drug (AED) administration. AED treatment is usually not recommended for the patients with a first attack, but should be considered for those with a second or third attack. A choice of AED has been based on the expert opinion. Carbamazepine (CBZ) is recommended for both acute and chronic treatment of seizure clusters in patients with BIS. Valproic acid (VPA), CBZ or clobazam (CLB) appears to be a first option of AED for patients with PS. A common first choice for BCECTS is CBZ in the USA and Japan, and VPA in the EU. The treatment period should be as short as possible without waiting for EEG normalization, possibly within 2 years after the initiation of AED. We must remember that some patients with BCECTS may have an "atypical evolution". In conclusion, when and how to treat this benign condition should be determined in an individual manner based on the length and frequency of seizures, circadian rhythm of the attacks, interictal EEG findings, cognitive and behavioral functions in daily life and the attitude of the parents toward seizure recurrences and AED side effects.

Keywords: Antiepileptic drug treatment; Benign focal epilepsies; Benign infantile seizures; Panayiotopoulos syndrome; Benign childhood epilepsy with centrotemporal spike

1. Introduction

Benign focal epilepsies represent almost one-fourth of all childhood epilepsies and are most frequently encountered not only in the clinical setting of pediatric neurology, but also in pediatric emergency medicine [1]. Compared to children with intractable epilepsy, those with benign focal epilepsies are believed to enter remission without antiepileptic drug (AED) treatment until adolescence [1–4]. The risks associated with chronic AED treatment might outweigh the risks seizure recurrences because the patients may experience only a few such recurrences. Thus, the issue of when and how to treat the patients has been a matter of debate for many years [2,3,5]. Consensus has been generally established in the context of the treatment of the child with a first unprovoked seizure in that patients without specific risk factors are recommended to postpone AED treatment at least until a second seizure [6]. In addition, there have been few evidence-based studies for the treatment of benign focal epilepsies, which makes it difficult to develop a formulated treatment policy [3,7]. In this article, I focus on the treatment of following three representative benign focal epilepsies, benign infantile seizures (BIS), Panayiotopoulos syndrome (PS) and benign childhood epilepsy with

* Address: Department of Pediatrics, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162, Japan. Tel.: +81 3 3353 8111; fax: +81 3 5269 7338.
E-mail address: hoguni@ped.twmu.ac.jp

0387-7604/$ - see front matter © 2010 The Japanese Society of Child Neurology. Published by Elsevier B.V. All rights reserved.
doi:10.1016/j.braindev.2010.10.024

centrotemporal spikes (BCECTS), because the prognosis of Gastaut type late-onset childhood occipital epilepsy has been shown to be unpredictable and the term "benign" is not included in this descriptive terminology [1].

2. Treatment for BIS

The concept of benign infantile convulsions (BIC) was first described by Fukuyama in 1963 [8]. He identified a group of previously normal infants who experienced one or a few clusters of generalized tonic-clinic seizures (GTCS), and later, the infants did not develop epilepsy. However, there was no progress for the concept of BIC until 1981 when Morooka reported 22 infants between 6 months and 2 years and 6 months of age who experienced a cluster of GTCS during periods of gastroenteritis with mild diarrhea [9]. This new syndrome received attention because of the close relationship between the seizures and rota gastroenteritis as well as the high incidence of this syndrome. In contrast, Watanabe et al. studied BIC with focal onset or secondarily generalized seizures from 1987 to early 1990's and proposed the concept of benign partial epilepsy in infancy, which was finally recognized as BIS in the 2001 International League Against Epilepsy (ILAE) classification [10]. At the same time, the syndrome of benign familial infantile convulsions (BFIS) proposed by Vigevano et al. was also recognized [11]. In the 2006 ILAE classification proposal, these two syndromes were combined and unified into one entity called BIS. Most recently, a new form of benign focal epilepsy termed benign familial neonatal-infantile seizures (BFNIS) has been established clinically and genetically, with an onset age between 2 days and 3.5 months of age, which nosologically link BIS to benign familial neonatal convulsions [12].

Thus, BIC as originally proposed by Fukuyama, came to include BIS and BIC with mild diarrhea, the latter of which has been recently re-designated as BIC with mild gastroenteritis (BICMG) and categorized as "chanced epilepsy". BICMG has not been recognized world-wide despite the fact that these seizures are the most common form of BIC in Japan. Sakauchi previously studied 56 infants with BIC, who showed two distinct peaks of onset age [13]. The earlier onset group was 2–11 months old, and they tended to have recurrent seizures or clusters of seizures that indicated BIS. In contrast, the later onset group was 1–2 years of age, and they experienced only one episode or one cluster of seizures, which indicated BICGM. Thus, the onset age and the association of mild diarrhea appear to be important for distinguish both conditions. The historical changes in the concept and terminology of BIS are shown in Fig. 1.

The treatments for BIS and BICMG can be categorized as acute or chronic (Table 1). Because the patients experience a cluster of seizures for several days, acute

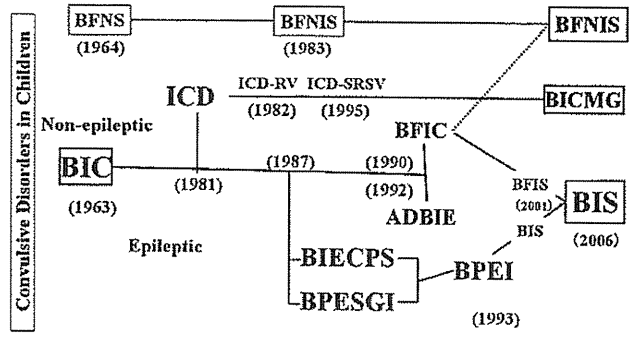

Fig. 1. Changes in the concept and terminology of benign infantile seizures (BIS)** by courtesy of Dr. Sakauchi. Abbreviations: BIC, benign infantile convulsions; ICD, infantile convulsions with diarrhea, ICD-RV, ICD with rotavirus infection; FCD-RV, febrile convulsions with diarrhea due to RV; BFIC, benign familial infantile convulsions; ADBIE, autosomal dominant benign infantile epilepsy; BPEI, benign partial epilepsy in infancy; BIECPS, benign infantile epilepsy with CPS; BPESGI, benign partial epilepsy with SG in infancy; BFNIS, Benign familial neonatal-infantile seizures; BICMG, Benign infantile convulsions with mild gastroenteritis.

treatment is urgent. There have been no control studies regarding the acute treatment for either syndrome. Intravenous or rectal diazepam therapy has been shown to be ineffective for seizure clusters [14–16]. There have been no systematic studies regarding rectal phenobarbital suppositories or intravenous phenytoin therapy. Intravenous lidocaine infusion therapy has been shown to suppress seizures effectively in a few open studies [14,15]. Most recently, single, low-dose oral CBZ has been shown control a cluster of seizures in patients with both BIS and BICGM. As such, CBZ appears to be the safest and easiest treatment option [16]. Although the evidence is limited, a single oral dosage of CBZ and an intravenous lidocaine infusion are currently recommended for the acute treatment of these seizures.

As for chronic prophylactic treatment, it is not generally recommended for patients with BICMG because the seizures seldom recur. In contrast, seizures in infants with BIS generally continue for months or years. The best AED and the best treatment duration have not been determined, although there was one open study recommending the use of low-dose CBZ in patients up to 2–3 years of age [16]. There were no available data for other agents such as PB or VPA, which have also been frequently used for infants with recurrent seizures. Thus, CBZ appears to be a first choice not only for the acute treatment of BICGM, but also chronic treatment of BIS.

3. Treatment for PS

PS is a benign age-related focal seizure disorder that occurs in early and mid-childhood. The onset age of epilepsy ranges from 1 to 14 years of age, with three-quarter of the cases occurring between 3 and 6 years. Clinical

Table 1
Antiepileptic drug (AED) treatment for benign focal epilepsies.

1. Treatment of benign infantile seizures (with or without mild gastroenteritis)
   (1) Acute AED treatment for a cluster of seizures: Administration of low-dose CBZ (5 mg/kg) once orally or through a nasogastric tube if infant is asleep.
   Intravenous infusion of lidocaine is an effective alternative if CBZ cannot be used or is not effective.
   Intravenous phenobarbital, phenytoin, and midazolam may be effective treatment
   Diazepam (i.v. or rectal usage) is not effective for a cluster of seizures.
   (2) Chronic AED treatment
   Benign infantile seizures with mild gastritis: Not required
   Benign infantile seizures: Low-dose CBZ (5 mg/kg) is recommended for use up to 2–3 years of age
2. Treatment of Panayiotopoulos syndrome
   (1) First seizure
   Prescribe a rectal diazepam suppository or solution for the next seizure and then postpone AED administration until at least a second seizure has occurred
   (2) Second or third seizure
   Start an AED if caregivers agree.
   VPA, CBZ or CLB is recommended.
   Those with frequent seizure recurrences* may require AED adjustment (e.g. high-dose VPA, CLB), *5–10% of patients, especially those with mild neurobehavioral disorders
   (3) Period of treatment
   Two to three years after the last seizure then discontinue AED without waiting for the disappearance of epileptic EEG spikes
3. Treatment of benign childhood epilepsy with centrotemporal spikes
   (1) Postpone AED administration until a second seizure occurs.
   (2) For short intervals between the first 3 seizures, a younger age of onset (less than 4 years), recurrent GTCS, or the presence of diurnal seizures are considered to be risk factors for seizure recurrences, thereby recommending the early initiation of AED
   (3) Selecting AEDs
   CBZ or VPA is recommended. Sulthiame, GBP and CLB are second options.
   (4) Period of treatment
   One to two years after the last seizure, AED should be discontinued without waiting for the disappearance of rolandic spikes
4. Treatment of atypical evolution of benign focal epilepsies (Atypical benign partial epilepsy of childhood)
   (1) Discontinue CBZ if it appears to provoke atypical evolution
   (2) Try ESM for spike-and-wave related absence seizures or epileptic negative myoclonus

seizures are characterized by sudden-onset autonomic symptoms including emesis, vomiting, and paleness of the face and the deviation of both eyes. These symptoms evolve to generalized tonic-clonic (generalized, unilateral), or prolonged atonic seizures, which are designated as ictal syncope. The seizures occur during sleep in two-third of all cases. Seizure duration is usually longer than 10 min, and 44% of patients develop status epilepticus lasting longer than 30 min. Interictal EEG shows high amplitude sharp or sharp-slow complexes recorded initially with posterior predominance, and shifting in localization or becoming multifocal along with an age progresses [1]. Some cases later show centro-temporal EEG foci, which are reminiscent of the foci shown in BCECTS. Other cases exhibited synchronous and asynchronous epileptic EEG foci between the frontopolar and parieto-occipital regions, which we have designated as the "Fp-O pattern" [17]. The prognosis of PS is excellent. Remission often occurs within one to two years after onset, and always occurs before 12 years of age. Roughly 5–10% of the patients may experience recurrences of either brief or prolonged autonomic attacks more than 6–10 times that are refractory to conventional AED therapy.

Fig. 2 illustrates the ages of 106 children with PS at the time of their first and last seizures [18]. The age range for the first seizure was from 1 to 10 years of age with a peak at 3–5 years of age. The ages at last seizures ranged from 3 to 10 years. A total of 77% of cases entered remission within 3 years from onset. Fifteen percent of the patients had only had a single seizure. However, 17 of the 106 cases (17%) had more than 10 seizure recurrences despite AED treatment. In our previous study, most of the latter cases had mild neurobehavioral abnormalities, which may have contributed to the refractoriness of seizures because the abnormalities were found before the onset of epilepsy [19]. However, all of the cases ultimately entered remission until 12 years of age.

Treatment of PS has not yet been well studied because of the condition's excellent prognosis. AED treatment is usually not recommended. However, a rectal diazepam suppository or solution should be better to be prepared for a next prolonged seizure. There have been no control studies nor open trials specifically for AED treatment of PS. There were two control studies for the newly diagnosed form of childhood epilepsy enrolled mostly patients with idiopathic focal epilepsy, thereby demonstrating the equal effectiveness between CBZ and VPA in one study, and also among phenobarbital (PB), phenytoin (PHT), CBZ and VPA in the other study [20,21]. Independent expert-consensus studies were conducted in the USA, EU and Japan in which

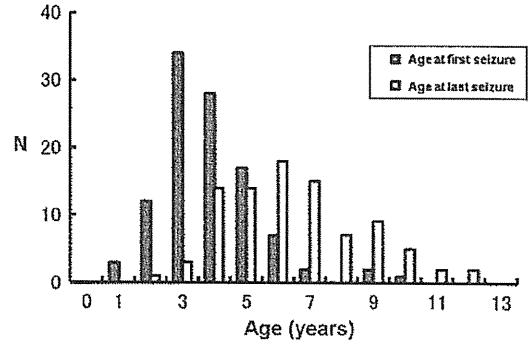

Fig. 2. The ages at the first and last seizures for 106 children with Panayiotopoulos syndrome followed-up at Tokyo Women's Medical University. The peak incidences of epilepsy onset and remission were 3–4 years and 5–7 years of age, respectively in the study cohort [18].

the treatment choice for children with cryptogenic complex partial epilepsy was oxcarbazepine (OXC) and CBZ, CBZ and OXC, and CBZ and zonisamide (ZNS), respectively [22–24]. In this regard, the choice of AED has to be determined based on the side-effect profiles of these agents. Thus, CBZ or VPA is usually recommended when AED is introduced in PS patients [25]. In rare instances, CBZ may paradoxically induce seizures and cause EEG exacerbation [26]. Most recently, Hirano et al. investigated the effectiveness of AEDs on seizures in 26 PS patients with more than six seizure recurrences. The effectiveness of both VPA, especially high-dose, and CLB appeared to be better than that of CBZ [27].

In conclusion, the prognosis of PS is excellent except for 5–10% of patients who have many seizure recurrences. AED treatment is usually not recommended for the patients with a first seizure. After a second or third seizure, it would be better consider treating patients with VPA, CLB or CBZ, depending on the length of seizures, the association of mild neurobehavioral disorders and whether parents are more concerned about seizure recurrences or chronic AED side effects.

4. Treatment for BCECTS

BCECTS is a prototype of idiopathic focal epilepsies and has been extensively studied with clinical, electrophysiological and genetical methods, although the molecular approach has not yet been successful. BCECTS, which comprises 15–20% of all childhood epilepsy cases, is the most common epileptic syndrome in children [1]. The onset age of epilepsy ranges from 3 to 13 years of age with peak incidence occurring between 9 and 10 years of age. Typical seizures are characterized by short-lasting focal motor or sensory seizures that occur exclusively during sleep. An EEG typically shows biphasic sharp wave discharges arising from centro-temporal regions during sleep (rolandic spikes). The prognosis is excellent. The seizures enter remission always before 10–12 years of age, and the rolandic spikes disappear before 15–16 years of age.

Bouma et al. conducted a meta-analysis of 20 publications for a total of 794 patients with BCECTS [5]. The study demonstrated that seizures occurred only once in 15.6% of the patients, two to five times in 62.1%, 6 to 15 times in 17.3% and more than 15 times in 5.3%. Thus, 77% of the patients had less than five seizure recurrences, similar to the figures for PS. Secondary GTCS occurred in 43.5% of the patients. A follow-up was successfully conducted without AED in 18.4% of the patients. AED treatment was successfully discontinued in 87.8% of the patients and seizure recurrences after AED discontinuation were found in 14.2% of the patients. Finally, seizure remission was confirmed in 97.7% of all patients. In conclusion, the authors stated that early prediction of seizure outcome in a new patient with BCECTS cannot be determined with certainty based on these meta-analyses. In other words, it is difficult to predict which patients have possible few seizure recurrences without requiring chronic AED treatment at the time of their first seizures.

Conversely, there have been several risk factors that suggest a longer duration of the active seizure period and frequent seizure recurrences. If short intervals exist between the first three seizures, a younger age of onset (less than 4 years), or a presence of recurrent GTCS and diurnal seizures, these characteristics indicate the need for early AED treatment [2,4,5].

Although the ultimate prognosis of BCECTS is excellent, recent neuropsychological studies using more sophisticated tests showed that rolandic spikes could interfere with specific cognitive and behavioral functions in children with BCECTS. Between 28% and 53% of children with BCECTS displayed neuropsychological abnormalities during the active phase of the epilepsy, including cognitive dysfunction such as difficulties with auditory-verbal, and visuospacial memory and executive function tasks as well as language impairment, attention disorders, learning disabilities, and behavioral disturbances [28]. However, we do not know whether the neuropsychological abnormalities are a consequence of persistent rolandic spikes or already existed before the onset of epilepsy. Whether chronic AED treatment could prevent these neuropsychological dysfunctions is also unknown.

The choice of AED for those with BCECTS is mostly based on expert opinions without any control studies. It is now generally accepted that AED administration should be postponed until at least a second seizure occurs. CBZ is recommended as a first-line AED in both USA and Japan, whereas VPA is the first-line AED in EU according to expert-consensus studies [22–24]. Sulthiame and gabapentin are AEDs effective for those with BCECTS as demonstrated by a randomized control study [3,7]. Sulthiame is not only effective for BCECTS seizures but also for rolandic spikes, although the effect may not be lasting long. Thus, CBZ or VPA is the best choice for clinical practice. Sulthiame and GBP are good second options (Table 1). Some authors recommend clobazam (CLB) or clonazepam (CZP) taken once before going to sleep, which can suppress not only seizures but also rolandic spikes [29]. However, the development of tolerance and sedative side effects remains a problem for these benzodiazepines. Although newly introduced AEDs including lamotrigine (LTG), OXC, topiramate (TPM) and levetiracetam (LEV) are also potentially effective and have fewer side effect, a large scale study is needed to determine whether they have superior effects compared to AEDs that have previously been described. For the time being, these medications should be considered as a second or third choice depending on the

side-effect profiles. AED treatment should be kept as short as possible. Usually the treatment lasts for 1–2 years after the last seizure, and then the treatment is discontinued without waiting for a disappearance of rolandic spikes.

5. Treatment for atypical forms of benign focal epilepsies

Benign focal epilepsies, especially, PS and BCECTS, occasionally show atypical features including severe aggravation of epileptic manifestations as well as transient or persistent impairments of cognitive, behavioral and language functions. Fejerman designated these forms of epilepsy as "atypical evolution" of benign focal epilepsies [25]. Although Landau-Kleffner syndrome and continuous spike-and-wave during slow sleep (CSWS) syndrome have nosologically been placed within a conceptual framework of begin focal epilepsies, the treatment of all of these ILAE-recognized epileptic syndromes is beyond the focus of this paper. However, the following two forms of "atypical evolution" are important.

5.1. Atypical benign partial epilepsy of childhood

During the clinical course of BCECTS, some patients develop frequent atonic drop attacks (mostly epileptic negative myoclonus) and display nearly continuous diffuse spike-and-wave during sleep which mimics CSWS, at times following the CBZ administration. The spike-and-wave related atonic or absence attacks may resolve spontaneously after stopping CBZ treatment but often continue over years if proper treatment is not introduced. We have recommended the early introduction of ethosuximide (ESM), and adrenocorticotropin (ACTH) or steroid therapy if ESM is insufficient [30].

5.2. Status of BCECTS

During the clinical course of BCECTS, some patients also develop frequent focal status epilepticus involving the oro-motor area, which leads to transient drooling, dysphasia, dysarthria or even aphasia. Some other children may develop the same symptoms along with worsening of EEGs associated with a few oro-motor seizures. Shafrir and Prensky recognized the latter condition as a new entity that was distinct from Landau-Kleffner syndrome and designated it as acquired epileptiform opercular syndrome [31]. In this condition, direct clinical or indirect electrical interference in the bilateral paraopercular regions has been suggested to inhibit the neuronal activity of the cortex integrating oro-motor functions. AED treatment has been shown to be difficult during the active phase of the epilepsy. Most recently, von Stulpnagel et al. reported a promising LEV effect for these atypical rolandic epilepsies [32].

6. Worsening of idiopathic focal epilepsies from CBZ treatment

There have been many case reports regarding the worsening of seizures and epileptic EEG abnormalities in children with idiopathic focal epilepsies shortly after the introduction of CBZ, as we previously described [33]. Because CBZ is always the first choice for the treatment of idiopathic and symptomatic focal epilepsies regardless of age, the paradoxical reactions of CBZ should always be considered. CBZ can potentially increase not only generalized spike-and-wave activity leading to aggravation of absence seizures but also accelerate the secondary bilateral synchrony producing CSWS in children with idiopathic focal epilepsies. Thus, CBZ is not recommended for patients with BCECTS that shows frequent spike-and-wave discharges while the patient is asleep or while the patient is awake.

7. Discussion

Because the prognosis has been shown to be excellent in patients with benign focal epilepsies, we must consider a balance between the risks and benefits of chronic AED treatment [1]. Treatment with AEDs has risks of acute and chronic side effects and is an economic burden. However, parents may be overly concerned about the recurrence of seizures if their child is not treated. In addition, recent studies have clarified a risk of potential cognitive and behavioral impairments caused by epileptic EEG spikes in children with benign focal epilepsies, which could be treated with AEDs [28]. However, it is not known whether AED treatment can effectively suppress epileptic EEG abnormalities without side-effects or even of the resulting decreases in the epileptic EEG abnormalities can reasonably improve cognitive and behavioral functions.

The attitudes of parents and physicians about whether we should treat or not treat a patient change depending on the circumstances of the individual patient because the epileptic conditions in children with benign focal epilepsies are not always homogeneous. Some cases have few seizure recurrences and rare epileptic EEG abnormalities, and other cases have several or more seizure recurrences and abundant epileptiform EEG abnormalities. Thus, rigid treatment recommendations are not always helpful for patients with benign focal epilepsies. Ultimately, the best goal for children with benign focal epilepsies is to make them a free from restrictions as possible so that they can lead a normal school life irrespective of AED treatment. Thus, when and how to treat this benign condition should be determined in an individual manner based on the length and frequency of seizures, circadian rhythms of the attacks,

the attitudes of the patients' parents toward seizure recurrences and AED side effects, interictal EEG information, and finally cognitive as well as behavioral functions in daily life.

Acknowledgement

This study was presented at the 10th Asian & Oceanian Congress of Child Neurology in Daegu, Korea, June 11, 2009.

References

[1] Panayiotopoulos CP. Benign childhood focal seizures and related epileptic syndromes. In: Panayiotopoulos CP, editor. A clinical guide to epileptic syndromes and their treatment. London : Springer-Verlag Ltd; 2007. p. 285–318.
[2] Ambrosetto G, Tassinari CA. Antiepileptic drug treatment of benign childhood epilepsy with rolandic spikes: is it necessary? Epilepsia 1990;31:802–5.
[3] Bourgeois BF. Drug treatment of benign focal epilepsies of childhood. Epilepsia 2000;41:1057–8.
[4] Loiseau P, Duche B, Cordova S, Dartigues JF, Cohadon S. Prognosis of benign childhood epilepsy with centrotemporal spikes: a follow-up study of 168 patients. Epilepsia 1988;29: 229–35.
[5] Bouma PA, Bovenkerk AC, Westendorp RG, Brouwer OF. The course of benign partial epilepsy of childhood with centrotemporal spikes: a meta-analysis. Neurology 1997;48:430–7.
[6] Arts WF, Geerts AT. When to start drug treatment for childhood epilepsy: the clinical-epidemiological evidence. Eur J Paediatr Neurol 2009;13:93–101.
[7] Rating D, Wolf C, Bast T. Sulthiame as monotherapy in children with benign childhood epilepsy with centrotemporal spikes: a 6-month randomized, double-blind, placebo-controlled study. Sulthiame study group. Epilepsia 2000;41:1284–8.
[8] Fukuyama Y, Arima M, Okada R, Suzuki M, Komiya H, Komiya K, et al. Electro-clinical characteristics of epilepsies in infancy and childhood. Paediatr Univ Tokyo 1963;59:11–6.
[9] Morooka K. Convulsions and mild diarrhea. Shonika (Tokyo) 1982;23:131–7, [in Japanese].
[10] Watanabe K, Yamamoto N, Negoro T, Takahashi I, Aso K, Maehara M. Benign infantile epilepsy with complex partial seizures. J Clin Neurophysiol 1990;7:409–16.
[11] Vigevano F, Fusco L, Di Capua M, Ricci S, Sebastianelli R, Lucchini P. Benign infantile familial convulsions. Eur J Pediatr 1992;151:608–12.
[12] Berkovic SF, Heron SE, Giordano L, Marini C, Guerrini R, Kaplan RE, et al. Benign familial neonatal-infantile seizures: characterization of a new sodium channelopathy. Ann Neurol 2004;55:550–7.
[13] Sakauchi M. A clinical, genetical and electroencephalogrphical study of benign infantile convulsions (FUKUYAMA). J Tokyo Womens Med Coll 1997;67:111–28.
[14] Okumura A, Uemura N, Negoro T, Watanabe K. Efficacy of antiepileptic drugs in patients with benign convulsions with mild gastroenteritis. Brain Dev 2004;26:164–7.
[15] Hattori H, Yamano T, Hayashi K, Osawa M, Kondo K, Aihara M, et al. Effectiveness of lidocaine infusion for status epilepticus in childhood: a retrospective multi-institutional study in Japan. Brain Dev 2008;30:504–12.
[16] Matsufuji H, Ichiyama T, Isumi H, Furukawa S. Low-dose carbamazepine therapy for benign infantile convulsions. Brain Dev 2005;27:554–7.
[17] Ohtsu M, Oguni H, Hayashi K, Funatsuka M, Imai K, Osawa M. EEG in children with early-onset benign occipital seizure susceptibility syndrome: Panayiotopoulos syndrome. Epilepsia 2003;44: 435–42.
[18] Hirano Y, Oguni H, Funatsuka M, Imai K, Osawa M. Clinical and EEG study of 106 children with Panayiotopoulos syndrome. J Jpn Pediatr Soc 2009;113:522–7, [in Japanese].
[19] Hirano Y, Oguni H, Funatsuka M, Imai K, Osawa M. Neurobehavioral abnormalities may correlate with increased seizure burden in children with Panayiotopoulos syndrome. Pediatr Neurol 2009;40:443–8.
[20] de Silva M, MacArdle B, McGowan M, Hughes E, Stewart J, Neville BG, et al. Randomised comparative monotherapy trial of phenobarbitone, phenytoin, carbamazepine, or sodium valproate for newly diagnosed childhood epilepsy. Lancet 1996;347: 709–13.
[21] Verity CM, Hosking G, Easter DJ. A multicentre comparative trial of sodium valproate and carbamazepine in paediatric epilepsy. The paediatric EPITEG collaborative group. Dev Med Child Neurol 1995;37:97–108.
[22] Oguni H, Hirano Y, Katoh I. Treatment of childhood epilepsies: Japanese Expert Consensus study and a comparison of the results with those of the USA and EU. No To Hattatsu 2010;42:262–6.
[23] Wheless JW, Clarke DF, Arzimanoglou A, Carpenter D. Treatment of pediatric epilepsy: European expert opinion, 2007. Epileptic Disord 2007;9:353–412.
[24] Wheless JW, Clarke DF, Carpenter D. Treatment of pediatric epilepsy: expert opinion, 2005. J Child Neurol 2005;20(Suppl. 1): S1–S56, quiz S9-60.
[25] Fejerman NCR. Early-onset benign childhood occipital epilepsy (Panayiotopoulos type). In: Benign focal epilepsies in infancy, childhood and adolescence. In: Fejerman NCR, editor. Current problems in epilepsy sereis, vol. 21. Montrouge: John Libbey Eurotext; 2007. p. 179–220.
[26] Kikumoto K, Yoshinaga H, Oka M, Ito M, Endoh F, Akiyama T, et al. EEG and seizure exacerbation induced by carbamazepine in Panayiotopoulos syndrome. Epileptic Disord 2006;8:53–6.
[27] Hirano Y, Oguni H, Osawa Makiko. Retrospective analysis of antiepileptic drugs effective for children with Panayiotopoulos syndrome. No To Hattatsu 2010;42:S204.
[28] Chahine LM, Mikati MA. Benign pediatric localization-related epilepsies. Epileptic Disord 2006;8:243–58.
[29] Mitsudome A, Ohfu M, Yasumoto S, Ogawa A, Hirose S, Ogata H, et al. The effectiveness of clonazepam on the Rolandic discharges. Brain Dev 1997;19:274–8.
[30] Oguni H, Uehara T, Tanaka T, Sunahara M, Hara M, Osawa M. Dramatic effect of ethosuximide on epileptic negative myoclonus: implications for the neurophysiological mechanism. Neuropediatrics 1998;29:29–34.
[31] Shafrir Y, Prensky AL. Acquired epileptiform opercular syndrome: a second case report, review of the literature, and comparison to the Landau-Kleffner syndrome. Epilepsia 1995;36:1050–7.
[32] von Stulpnagel C, Kluger G, Leiz S, Holthausen H. Levetiracetam as add-on therapy in different subgroups of "benign" idiopathic focal epilepsies in childhood. Epilepsy Behav 2010;17:193–8.
[33] Guerrini R, Belmonte A, Genton P. Antiepileptic drug-induced worsening of seizures in children. Epilepsia 1998;39:S2–S10.

BRAIN and NERVE 63(4) : 393-400, 2011

特 集 ■ てんかんの新しい治療

小児難治性てんかんに対するケトン食療法
——「最後の選択肢」から「早期からの選択肢」へ

A Ketogenic Diet for Intractable Childhood Epilepsy; As an Early Option as well as a Last Resort

伊藤　進*　小国弘量*

Susumu Ito*, Hirokazu Oguni*

Abstract

Since the 1920s, a ketogenic diet, of low-carbohydrate, adequate-protein and high-fat content, has been used for the treatment of intractable childhood epilepsy. A decade ago this diet was tried as a last resort in the treatment of intractable epilepsy. However, recent advances in ketogenic diet have enabled it to become more commonly used worldwide even early in the course of epilepsy. Two less-restrictive ketogenic diets, namely, the modified Atkins diet and low-glycemic-index treatment, have been developed. These diets allow the patients and their families to choose a more liberal menu. Furthermore, a randomized controlled trial found that the ketogenic diet has a significant benefit, which strengthens the supportive evidence. Recently, an international consensus statement guiding optimal clinical management has been published, allowing clinicians to provide standardized treatment. There has also been increased interest in investigating the mechanisms of action of ketogenic diet using various experimental models. The authors review the history, efficacy, side effects, and possible mechanisms underlying the ketogenic diet, as well as the experience with the ketogenic diet at Tokyo Women's Medical University.

Key words : ketogenic diet, medium-chain triglycerides, MCT, modified Atkins diet, low-glycemic-index treatment

はじめに

小児てんかんに対する治療は成人のそれと同様であり，てんかん発作型やてんかん症候群に基づき抗てんかん薬を選択していく[1-3]。しかし，乳幼児期に発症するてんかんの中には，非常に難治に経過するてんかんや，さらにはてんかん性脳症（epileptic encephalopathy）といわれる脳機能の進行性障害により重篤な認知障害や行動障害をもたらすとされるてんかんもある[4,5]。それらの難治性てんかんに対しては，種々の抗てんかん薬治療のみならず，適応があれば外科治療も選択される[6]。また，食事療法の一種である「ケトン食療法」も治療選択肢となる[7-13]。

ケトン食療法は低炭水化物および高脂質の特殊な食事療法であり，従来は患者とその家族のみならず医療者にも難解で困難な最後の選択肢（last resort）であった。しかし，最近になり，制限を緩和したケトン食療法が相次いで考案され，忍容性が改善しつつある[14,15]。また，ケトン食療法の有効性を証明した無作為化比較試験の結果も報告され，近年のエビデンスを重視する医療においても有効な治療法の１つとしての地位が確立しつつある[11]。さらに，世界各国の小児てんかん専門医らで構成されるコンセンサスグループよりケトン食療法に関する推奨事項が公表され，プロトコールの標準化も進みつつある[12]。本稿では古くて新しいてんかん治療法であるケトン食療法につき概説する。

* 東京女子医科大学小児科学〔〒162-8666　東京都新宿区河田町 8-1〕Department of Pediatrics, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan

1881-6096/11/¥500/論文/JCOPY