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．

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FULL-LENGTH ORIGINAL RESEARCH

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

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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

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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

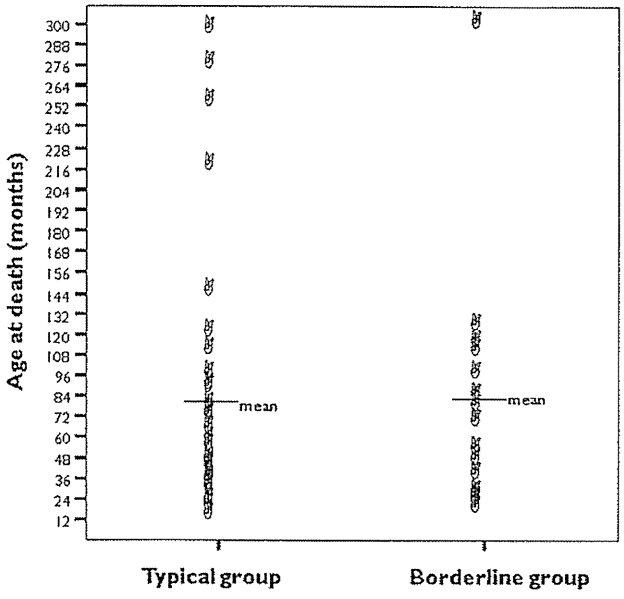

Figure 1.
Dot plots showing the distribution of age at death in the typical and borderline groups (n = 59). The age at death appeared prevalent between 13 and 140 months of age and sparse thereafter in both typical and borderline groups. No significant difference was observed between these two groups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

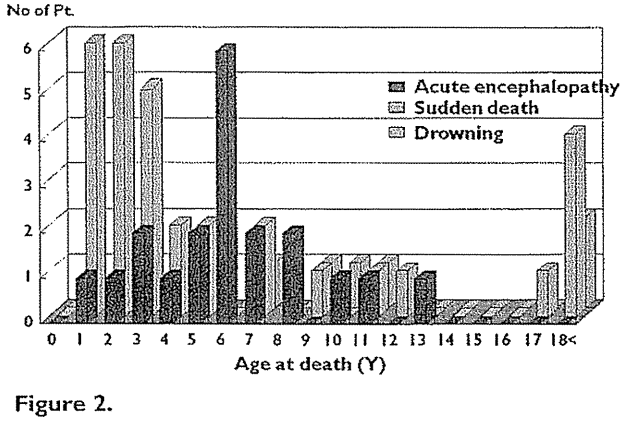

Figure 2.
Distribution of ages at death with respect to the causes of mortality. The incidence of sudden death reached a first peak at 1–3 years old and a second small peak at 18 years and older. In contrast, the acute encephalopathy-related mortality rate reached a sharp peak at 6 years old. All patients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

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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.

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Appendix

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Review article

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

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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

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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

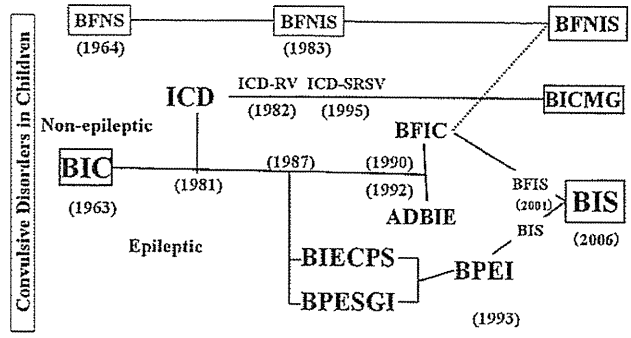

Fig. 1. Changes in the concept and terminology of benign infantile seizures (BIS)** by courtesy of Dr. Sakauchi. Abbreviations: BIC, benign infantile convulsions; ICD, infantile convulsions with diarrhea, ICD-RV, ICD with rotavirus infection; FCD-RV, febrile convulsions with diarrhea due to RV; BFIC, 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

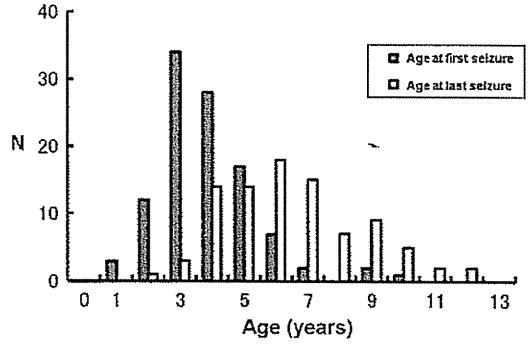

Fig. 2. The ages at the first and last seizures for 106 children with Panayiotopoulos syndrome followed-up at Tokyo Women's Medical University. The peak incidences of epilepsy onset and remission were 3–4 years and 5–7 years of age, respectively in the study cohort [18].

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.

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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

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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。

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Ⅰ．てんかんに対する食事療法の歴史

1．ケトン食療法の発展と衰退

てんかんに対する食事療法の歴史は紀元前にまで遡る。古代ギリシアの医師であるHippocratesは断食によりてんかん発作が抑制された症例を記述しており，また，新約聖書にもてんかん発作の治療には祈りと断食が必要であることが記述されていた[16]。20世紀初頭に入り，1911年にフランスの内科医であるGuelpaとMarieが20名のてんかん患者に対し4日間の絶食が発作の抑制に有効であることを報告した[17]。その後，1921年にアメリカの内分泌科医であるGeyelinが，整骨医のConklinが実践していたてんかん患者に対する絶食を参考に，20日間に及ぶ絶食により26名中20名の患者で発作が改善したことを報告した[18]。さらに，同年にシカゴのWoodyattが絶食もしくは極端な低炭水化物および高脂質の食事の摂取によりケトン体が生成されることを報告し[19]，同時期にMayoクリニックのWilderも低炭水化物および高脂質の食事によるケトン血症がてんかん患者に絶食と同様の効果を発揮することを見出し[20]，この食事療法は「ケトン食療法（ketogenic diet）」と命名された。その頃から，ケトン食療法の1日あたりの組成は10～15 gの炭水化物，体重あたり1 gの蛋白質，ほかは脂質であり，現在の組成とほぼ同様であった[21]。当時，抗てんかん薬は臭化カリウムとフェノバルビタールの2種類のみであり，ケトン食療法は新たな治療法として幅広く使用されるようになった。しかし，1938年にジフェニルヒダントインの有効性が報告されたことを契機に医師や研究者の関心は抗てんかん薬に向くようになり，さらに1967年には全般てんかんに有効なバルプロ酸ナトリウムが発売され，その後も新たな抗てんかん薬が次々と開発，使用されるようになり，ケトン食療法は徐々に使用されなくなっていった。その後，1971年にはChicago大学のHuttenlocherが中鎖脂肪酸（medium-chain triglycerides：MCT）オイルを使用したケトン食療法の変法を考案するなど改良も図られたが[22]，なおケトン食療法は一部の施設でのみ実施可能な特殊な治療法となっていった。

2．ケトン食療法の復興

ケトン食療法の復興はひとりの小児難治性てんかん患者が端緒となった。1993年のこと，2歳の男児Charlieのてんかん発作は種々の抗てんかん薬治療や外科治療にも関わらず非常に難治に経過していたが，Johns Hopkins大学にたどり着きケトン食療法を開始したところ即座に抑制された（Charlieの経過の詳細はhttp://www.charliefoundation.org/を参照されたい）。Charlieの父親はCharlie基金を設立してケトン食療法の臨床研究の支援[7]，書籍発刊の支援[23]，映画の製作（“First Do No Harm”，邦題：「誤診」）を通じた啓蒙活動を行い，また，その経緯が雑誌やTVで紹介されたことにより，ケトン食療法は再び広く知れ渡るようになった。また，1998年には血液中から脳内にグルコースを輸送するグルコース輸送担体1型（glucose transporter type 1：GLUT1）の異常によるGLUT1欠損症が報告され，ケトン食療法が代替エネルギー源としてのケトン体を確保するための唯一の治療法であることからも医療者の注目を集めるようになった[24]。その後，ケトン食療法の変法も相次いで報告され，2003年にはJohns Hopkins大学のKossoffらがアトキンス食変法（modified Atkins diet）を[14]，2005年にはHarvard大学のPfeiferとThieleが低グリセミック指数食療法（low-glycemic-index treatment）を考案した[15]。それらの結果，現在ではケトン食療法は世界45カ国以上で使用されるに至り[25]，米食文化のアジア圏においても韓国を中心に積極的に使用されてきている[9,26-30]。

Ⅱ．ケトン食療法の機序

ケトン食療法の発見からおよそ1世紀が経過しようとしているにもかかわらず，抗けいれん作用の機序についてはいまだに解明されていない。しかし，さまざまな臨床研究および基礎研究が報告されており，ケトン体，低炭水化物，不飽和脂肪酸などによる複合的な機序が推定されている。

1．ケトン体による抗けいれん作用

ケトン体はβ-ヒドロキシ酪酸（beta-hydroxybutyrate），アセト酢酸（acetoacetate），アセトン（acetone）の総称であり，飢餓状態において肝臓で脂肪酸からβ酸化により生成される。血中β-ヒドロキシ酪酸濃度はてんかん発作の抑制とある程度の相関が報告されていることから治療効果を確認する1つの指標とされており，血中アセト酢酸濃度も同様に相関が報告されている[31,32]。しかし，てんかん動物モデルでは，アセト酢酸濃度と発作の抑制との相関は報告されているものの[33]，β-ヒドロキシ酪酸濃度とは相関が確認されていない[34]。また，*in vitro*モデルでは，両者ともラットの海馬組織において興奮性シナプス後電位（excitatory postsynaptic poten-

tial)を変化させず，直接の抗けいれん作用は確認されなかった[35]。しかし，最近になり，両者によりマウスおよびラットの黒質網様部の神経細胞の自然発火頻度が減少し，ATP(adenosine triphosphate)感受性カリウムチャネル阻害薬の存在下および同ノックアウトマウスにおいては同様の現象を認めなかったことが報告され，同チャネルを介した抗けいれん作用が提唱されている[36]。また，揮発性のアセトンについてもてんかん動物モデルにおいて抗けいれん作用が報告されている[37]。

2．低炭水化物による抗けいれん作用

ケトン食療法においては炭水化物が制限されることから，低炭水化物による抗けいれん作用も推定されている。実際に，本仮説により考案された低グリセミック指数食療法においては，てんかん発作の抑制は血中β-ヒドロキシ酪酸高値とは相関せずに血糖低値と相関したと報告されている[38]。最近になり，2-deoxyglucose (2-DG) というグルコースリン酸イソメラーゼ (phosphoglucose isomerase) の阻害により解糖を抑制するグルコース類似物質が，いくつかのてんかん動物モデルにおいて発作を抑制することが報告され注目されている[39,40]。また，前述のATP感受性カリウムチャネルは，グルコース制限下において細胞内ATP減少により開孔して過分極させることが報告されており，けいれん閾値を上昇させると推定されている[41]。

3．不飽和脂肪酸による抗けいれん作用

ケトン食療法により多価不飽和脂肪酸の一種であるドコサヘキサエン酸 (docosahexanoic acid) やアラキドン酸 (arachidonic acid) などが血中で上昇し[42]，総脂肪酸値は発作の抑制と並行しているとの報告もある[43]。ドコサヘキサエン酸やエイコサペンタエン酸 (eicosapentaenoic acid) はマウスの海馬においてけいれん閾値を上昇させることが報告されており，ナトリウムチャネルやカルシウムチャネルの阻害による機序が推定されている[44]。

III．ケトン食療法の適応と禁忌

1．ケトン食療法の適応

最近になり，Charlie基金より委託された9カ国26名の小児てんかん専門医および栄養士から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た[12]。それによると，年齢および性別にかかわらず，2種類ないし3種類の抗てんかん薬が無効であった小児難治性てんかん患者，特に症候性全般てんかんの患者においては，ケトン食療法の導入を積極的に考慮すべきとしており，「最後の選択肢」から「早期からの選択肢」となりつつある。また，前述のGLUT1欠損症とミトコンドリア病のうちピルビン酸脱水素酵素複合体 (pyruvate dehydrogenase complex：PDHC) 欠損症の患者においては，ケトン体が脳への代替エネルギーとなるため有効な治療選択肢としている。一方，外科治療の適応となる小児難治性てんかん患者に対する効果は限定的とされている。

2．ケトン食療法の禁忌

長鎖脂肪酸はミトコンドリア内に輸送された後にβ酸化によりアセチルCoAを生成し，トリカルボン酸 (tricarboxylic acid：TCA) 回路によりエネルギー産生される一方で，肝臓においてケトン体も生成される。よって，脂肪酸輸送障害およびβ酸化異常症では禁忌であり，ケトン食療法の導入前に鑑別除外する必要がある。また，PDHC欠損症以外のミトコンドリア病でも禁忌とされているが，安全に実施できたとする報告もある[12,28]。

IV．ケトン食療法の種類 (Table 1)

1．古典型ケトン食療法

古典型ケトン食療法 (classical ketogenic diet) は現在も最もよく使用されているケトン食療法であり，脂質に対する炭水化物と蛋白質を合わせた重量の比率を4対1ないし3対1とした組成とし，総熱量を約75%，水分量を80～90%に制限する。糖質を厳格に制限するため，使用中の抗てんかん薬を含む内服薬自体に糖質成分が含有されている場合には含有されていない剤型などに変更する。また，ビタミンおよびカルシウムが不足するため，総合ビタミン薬およびカルシウム薬を処方する。48時間前後の絶食期間ののちにケトン食を開始し，1～2日以内に全量を摂取できるようにする方法が一般的である。1998年のViningらによる多施設共同前方視的研究においては，4対1ケトン食療法の開始3カ月後および1年後の効果は，発作消失がおのおの51名中6名 (12%) および同5名(10%)，90%以上の発作減少がおのおの計15名 (29%) および計11名 (22%)，50%以上の発作減少がおのおの計28名 (55%) および計20名 (39%) であった[7]。2003年のCochraneレビューでは，無作為化比較試験がないために信頼できるエビデンスはないと結論づけられていたが[45]，2008年にNealらによる無作為化比較試験によりその有効性が証明された[11]。本研究では，2～

Table 1　ケトン食療法の比較

ケトン食療法の種類	古典型ケトン食療法	MCT ケトン食療法	アトキンス食変法	低グリセミック指数食療法
報告者	Wilder	Huttenlocher ら	Kossoff ら	Pfeifer と Thiele
(報告年)	(1921 年)[20]	(1971 年)[22]	(2003 年)[14]	(2005 年)[15]
脂質：炭水化物＋蛋白質	4：1	1.2：1	1.5：1	0.7：1
脂質 ＊1	80%	MCT：45%＋LCT：10%	60%	40%
炭水化物 ＊1	5%	30%	10%	15%
蛋白質 ＊1	15%	15%	30%	45%
評価期間	12 カ月[7,8,11]	12 カ月[11]	6 カ月[52]	12 カ月（＊2）[38]
50%以上発作減少（＊3）	18～50%	22%	65%	継続患者の 66%
90%以上発作減少（＊4）	10～27%	10%	35%	継続患者の 44%
発作消失	5～10%	4%	19%	N. S.
継続率	30～55%	35%	80%	N. S.
特徴	・標準の方法 ・制限が厳格 ・長期評価が確立	・MCT オイルを使用 ・炭水化物・蛋白質制限を緩和 ・胃腸障害が高頻度とされる	・体重減量法を応用 ・炭水化物制限，脂質推奨のみ ・長期評価が未確立	・血糖上昇抑制効果を応用 ・食品種類・炭水化物制限のみ ・長期評価が未確立

＊1：重量比ないし重量%　＊2：後方視的研究　＊3：90%以上発作減少及び発作消失を含む　＊4：発作消失を含む
〔略語〕MCT：中鎖脂肪酸　LCT：長鎖脂肪酸　N. S.：記載なし

16 歳までの 145 名の小児難治性てんかん患者が無作為に振り分けられ，ケトン食療法群の 73 名のうち，さらに 37 名が 4 対 1 ないし 3 対 1 ケトン食療法，36 名が MCT ケトン食療法に振り分けられた。開始 3 カ月後にケトン食療法群 54 名および対照群 49 名が解析され，発作頻度はおのおの 62.0%および 136.9% ($p<0.0001$) と有意に減少し，50%以上の発作減少はおのおの 28 名 (38%) および 4 名 (5%) ($p<0.0001$)，うち 90%以上の発作減少はおのおの 5 名 (7%) および 0 名 ($p=0.058$) であった。一方，5 名は患者ないし家族の拒否，4 名は副作用によりケトン食療法を継続できなかった。ほかの研究においても，ケトン食療法の継続率は半年後で 70%前後，1 年後で 50%前後と報告されている[7,8]。

ケトン食療法の副作用としては胃腸障害が多く，ほかに脱水，低血糖，電解質異常，高脂血症，高尿酸血症，腎結石，成長障害などが挙げられている[26,46]。最近になり，ケトン食導入前の絶食期間を省略しても開始 3 カ月後の効果が同等で，かつ，脱水や低血糖の副作用が有意に減少したと報告された[27,47]。コンセンサスグループでは意見が一致しなかったが，効果の短期間での発現を重視する場合には副作用に留意しながら絶食とし，長期的な効果を重視する場合には絶食は不要としている[12]。

2．MCT ケトン食療法

MCT は長鎖脂肪酸と比較してケトン体をより生成しやすい。この性質に基づき[48]，Huttenlocher らは古典型ケトン食療法の忍容性の改善を目的に MCT ケトン食療法を考案した[22]。MCT ケトン療法では総熱量の 60%を MCT オイルより摂取し，脂質に対する炭水化物と蛋白質を合わせた重量の比率を 1.2 対 1 とすることにより，炭水化物および蛋白質の制限を緩和している。その後の 4 対 1 ケトン食療法との比較研究においてもてんかん発作の抑制の効果は同等であったが[49]，副作用として胃腸障害の頻度が多く使用は限られていた。しかし，2009 年の Neal らの主に 4 対 1 の古典型ケトン食療法との無作為化比較試験においては，効果ならびに忍容性は同等であったと報告されている[50]。

3．アトキンス食変法

体重減量法の 1 つであるアトキンス食療法 (Atkins diet) に基づき[51]，2003 年に Kossoff らは炭水化物以外の制限を排除したアトキンス食変法を考案した[14]。アトキンス食変法では炭水化物を 1 日 10～20 g に制限し脂質摂取を推奨するのみで，蛋白質，総熱量，水分は制限せず，絶食期間も不要としている。2003 年に 7～52 歳まで 6 名の難治性てんかん患者において，2 名で発作消失，さらに 1 名で 90%以上の発作減少を報告した。さらに，2006 年には 3～18 歳までの 20 名の小児難治性てんかん患者において施行している。その結果，開始 6 カ月後も継続できた 16 名 (80%) のうち，4 名 (25%) で発作消失，計 7 名 (44%) で 90%以上の発作減少，計 13 名 (81%) で 50%以上の発作減少を報告し，古典型ケトン食療法と

Table 2　東京女子医科大学病院小児科におけるケトン食療法の成績

報告者（報告年）	田島（1977年）[55,56]		福山ら（1984年）[57]		小国ら（2009年）[58]	
対象期間	1968～1973年		1982～1984年		1984～2007年	
患者数	51名		21名		54名	
患者年齢	2～11歳（中央値4歳）		6カ月～11歳（平均5歳1カ月）		6カ月～15歳（中央値4歳）	
方法	4：1ケトン食療法		MCTケトン食療法		MCTケトン食療法（42名） 4：1ケトン食療法（12名）	
評価期間	12カ月	24カ月	12カ月	24カ月	12カ月	
50%以上発作減少（＊1）	24名（47%）	11名（22%）	7名（33%）	6名（29%）	15名（36%）	4名（33%）
90%以上発作減少（＊2）	17名（33%）	8名（16%）	N. S.	N. S.	N. S.	N. S.
発作消失	N. S.	N. S.	3名（14%）	2名（10%）	6名（14%）	1名（8%）
継続率	26名（51%）	13名（25%）	17名（81%）	8名（38%）	25名（46%）	
てんかん発作型別もしくはてんかん症候群別による50%以上発作減少	全般性強直間代発作	4/6名（67%）	全般性強直間代発作	1/3名（33%）	症候性全般てんかん	2/17名（12%）
	ミオクロニー発作	15/23名（65%）	ミオクロニー発作	3/3名（100%）	症候性焦点性てんかん	2/8名（25%）
	点頭スパズム	4/6名（67%）	強直発作	4/8名（50%）	全般＋焦点性発作てんかん	3/3名（100%）
	失立発作	5/10名（50%）	脱力発作	1/2名（50%）	West → Lennox-Gastaut症候群移行型	4/5名（80%）
	焦点性発作	0/3名（0%）	非定型欠神発作	2/5名（40%）	Lennox-Gastaut症候群	1/5名（20%）
	複雑部分発作	2/3名（67%）	複雑部分発作	4/6名（67%）	Dravet症候群	6/13名（46%）
			二次性全般化発作	3/5名（60%）	ミオクロニー失立てんかん	1/3名（33%）

＊1：90%以上発作減少及び発作消失を含む　＊2：発作消失を含む
〔略語〕MCT：中鎖脂肪酸　N. S.：記載なし

同等の効果と忍容性の改善の可能性につき言及している[52]。また，2008年には18～53歳の30名の成人患者においても炭水化物を15 gとして実施し，開始1カ月後および3カ月後に14名（47%），6カ月後に10名（33%）の患者で50%以上の発作減少を報告している[53]。

4．低グリセミック指数食療法

グリセミック指数（glycemic index）は1981年にJenkinsらにより提唱され，各食品について炭水化物50 g相当を摂取したのち2時間の血糖値・時間曲線下面積から，グルコース50 gを摂取した際の面積を100とした比率として算出する[54]。例えば，白米やパンは約70%，野菜類も約70%，フルーツ類は約50%，牛乳やヨーグルトは約35%，乾燥豆類は約30%などと報告している。2005年にPfeiferとThieleは，食品の種類をグリセミック指数50%未満のものに制限した低グリセミック指数食療法により，11名の難治性てんかんの患者において，4名（36%）で発作消失，計8名（73%）で50%以上の発作減少，また，ケトン食療法より変更した9名の患者において，1名（11%）で発作消失，6名（67%）で発作減少を維持，2名（22%）で発作増悪を報告した[15]。その後，2009年にMuzykewiczらは主に難治性のてんかん患者76名において，食品をグリセミック指数50%未満，炭水化物を1日40～60 gに制限することを指導し，1カ月間継続患者の42%，1年間継続患者の66%で50%以上の発作減少を報告した。また，効果は血中β-ヒドロキシ酪酸高値とは相関せずに血糖低値と相関し，副作用として3名の患者に倦怠を認めたのみであったが，24%の患者は食事制限の困難さにより継続できなかったとも報告した[38]。コンセンサスグループは，前述したアトキンス食変法とこの低グリセミック指数食療法は青年患者および成人患者に有益であるとしている[12]。

V．当科におけるケトン食療法の実施

当科においては，1968年より古典型ケトン食療法を導入し[55,56]，1982年からはMCTケトン食療法も導入している[57,58]。さらに，2007年からはアトキンス食変法も導

入し，GLUT1 欠損症へも応用している[59]。当科におけるケトン食療法の治療成績を Table 2 に提示する。

おわりに

主に小児難治性てんかんに対して使用されているケトン食療法について，その発見から復興までの歴史，推定されている作用機序，適応と禁忌，おのおのの方法と成績，当科における成績などを概説した。従来は「最後の選択肢」の場合が多かったが，忍容性を改善した変法が考案され，また無作為化比較試験の結果よりその有効性がエビデンスとして確立され，コンセンサスグループによりその標準化が進められたことにより，世界的に小児難治性てんかんに対する「早期からの選択肢」となりつつある。また，本邦と同様に米食文化を主体とするアジア圏においても積極的に使用されるようになっている。しかしながら，本邦においては 1960～70 年代にかけて数多くの施設でこのケトン食療法が実施されていたものの，欧米と同様に使用頻度がいったん減少した後は再度復興することなく現在に至っている。最近になり，てんかん外科手術数の増加や新規抗てんかん薬の導入により欧米との格差は縮まりつつあるが，ケトン食療法に対する考え方にはいまだ大きな隔たりがあるようである。今後は本邦においても「最後の選択肢」ではなく「早期からの選択肢」として多くの専門施設で実施可能となることを期待したい。

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