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Original article

# A ten-year follow-up cohort study of childhood epilepsy: Changes in epilepsy diagnosis with age

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**Abstract**

*Objective:* To elucidate all of the characteristics of childhood epilepsy, we performed a long-term follow-up study on the patients who visited Okayama University Hospital.

*Subjects and methods:* We retrospectively investigated the patients who were involved in the previous epidemiological study and visited Okayama University Hospital for a period of 10 years after December 31, 1999.

*Results:* Overall, there were 350 patients' medical records that were evaluated, and 258 patients with complete clinical information available for a 10-year period were enrolled. Ten patients died and the remaining 82 were lost to follow-up. Of 258 patients with complete information, 153 (59.3%) were seizure-free for at least 5 years. One hundred thirty (50.4%) had intellectual disabilities and 77 (29.8%) had motor disabilities, including 75 (29.1%) with both disabilities on December 31, 2009. Thirty-four patients of 350 (9.7%) changed the epilepsy classification during follow-up. With regard to ten patients who died, nine of them had symptomatic epilepsy, particularly those with severe underlying disorders with an onset during the first year of life.

*Conclusion:* Clinical status considerably changed during the decade-long follow-up period in childhood epilepsy. Changes in the epilepsy diagnosis are especially important and should be taken into account in the long-term care of children with epilepsy.


*Keywords:* Epilepsy; Clinical course; Longitudinal study; Childhood

## 1. Introduction

To determine all of the characteristics of childhood epilepsy, it is important to investigate its epidemiology not only on a single prevalence day but also the detailed clinical course of the affected patients over a long period after the prevalence day, because epilepsy is chronic and includes heterogeneous disorders with variable outcomes. Epidemiological studies of childhood epilepsy have been undertaken in various countries [1–7]. However, there have been few such studies with long-term follow-up for childhood epilepsy in Japan [8]. Most of the published long-term follow-up epidemiological studies assessed outcomes in terms of remission or death [8–13], and there are only a few studies on the course of epilepsy including changes in classification [14,15].

It is possible that diagnosis of epilepsy classification may be changed because of age-dependent changes and/or identification of previously unknown etiology through advances in neuroimaging and genetic examination. Thus, we aimed to clarify the long-term course of

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childhood epilepsy in Japan from an epidemiological perspective. Oka et al. performed a large-scale population-based survey of childhood epilepsy in Okayama Prefecture, Japan using the prevalence day of December 31, 1999 [7]. Based on this study, we followed patients who had visited Okayama University Hospital for a period of 10 years. We aimed to disclose the decade-long burdens of childhood epilepsy on the patients, their family and society in this study.

## 2. Subjects and methods

### 2.1. Patients

Our previous neuroepidemiological survey of childhood epilepsy was based on all children aged <13 years living in Okayama Prefecture, Japan [7]. The prevalence day was December 31, 1999. The prevalence rate and distribution of epilepsy and epileptic syndromes were reported according to the classification by the International League Against Epilepsy (ILAE) in 1989 [16]. In this previous study, we determined that the patients who had taken antiepileptic drugs (AEDs) and/or who had experienced at least one seizure during the last five years had active epilepsy. Of the 2220 identified patients with active epilepsy, 510 (289 males, 221 females) had visited the Department of Child Neurology at Okayama University Hospital at least once, and clinical information was available after the prevalence day for 350 patients. Out of the 350 patients, 82 were lost to follow-up during the 10-year period after December 31,1999. In the present study, we performed a follow-up investigation of the remaining 268 patients (composed of Group 1, which contained 258 live patients, and Group 2, which contained 10 who died during follow–up) to clarify their detailed, clinical course of epilepsy, seizure outcomes, and disability. We used the same definition of active epilepsy as the previous study for consistency. Similarly, we also used the same ILAE 1989 classification [16], but new diagnostic entities such as Panayiotopoulos syndrome (PS) were included according to Berg et al. [17]. This study was approved by the Okayama University Ethics Committee with the following stipulation: investigation of patients who visited the Okayama University Hospital was approved but that of patients who did not visit this hospital was not permitted as a condition of ethics approval for the initial study.

### 2.2. Statistical analysis

We performed the Wilcoxon signed-rank test to compare the frequency of seizures and the number of AEDs between 1999 and 2009. The frequency of seizures (no seizure $\geqslant$5 years, no seizure for >1 year and <5 years, yearly, monthly, weekly, daily) was ranked as indices 1 through 6, and the number of AEDs (zero, one, two, three, four or more) as indices 1 through 4 (Table 4). We used SPSS Statistics (Japanese ver. 23; IBM Japan, Ltd., Tokyo, Japan) for this analysis.

## 3. Results

### 3.1. Group 1 patients

Distribution of the epilepsy classification in the 258 patients in 1999 and 2009 is shown in Table 1 and Supplementary Fig. 1: 163 and 163, respectively, were diagnosed with localization-related epilepsy, 72 and 68, respectively, with generalized epilepsy, and 14 and 19, respectively, with epilepsies undetermined (either focal or generalized). Sufficient information to make an epilepsy classification was not available for nine and eight patients, respectively.

With respect to the age distribution pattern, five (1.9%) patients were under one year of age, 55 (21.3%) were 1–4 years old, 124 (48.1%) were 5–9 years old, and 74 (28.7%) were 10–12 years old in 1999.

The mean age of the 258 patients was 7 years 7 months (range, 3 months–12 years 11 months) on December 31, 1999. The mean age at onset of epilepsy was exactly 3 years (range, 0 months–11 years 10 months), and 87 patients (33.7%) had an initial seizure during the first year of life.

Patients' underlying diseases are listed in Table 2 and include perinatal complications, cerebral dysgenesis/tumor, neurocutaneous syndromes, cerebrovascular disorder, genetic neurologic disease, sequelae of the central nervous system infection and hypoxic-ischemic encephalopathy. Etiologies were newly identified during follow-up in nine patients including focal cortical dysplasia (FCD) in three, *SCN1A* mutations in three, hippocampal sclerosis in two, and dysembryoplastic neuroepithelial tumor (DNT) in one. In addition, hippocampal sclerosis developed after encephalitis during follow-up in one patient. On December 31, 2009, no underlying diseases were found in the remaining 159 (61.6%) patients including 54 (20.9%) with only a family history of genetic factors for epilepsy or febrile seizures.

Diagnosis of epilepsy classification was changed during follow-up in 26 patients as shown in Table 3. One patient diagnosed with idiopathic localization-related epilepsy (ILRE; childhood epilepsy with occipital paroxysms) on the prevalence day was re-diagnosed with PS by 2009. Of 82 patients diagnosed with symptomatic localization-related epilepsy (SLRE) on the prevalence day, two showed evolution to different types of epilepsy (one to Lennox-Gastaut syndrome [LGS] and the other to epilepsy with continuous spike-waves during slow-wave sleep [ECSWS]). Another patient who, from infancy, had seizures that were often associated with fever but was still in the early phase of the disease on

Table 1
Epilepsy classification.

| | Group 1 ($n = 258$) | | Group 2 ($n = 10$) | |
|---|---|---|---|---|
| | December 31, 1999 | December 31, 2009 | December 31, 1999 | Death |
| Localization-related epilepsy | 163 (63.2%) | 163 (63.2%) | 5 (50.0%) | 4 (40.0%) |
| *Idiopathic* | *9* | *10* | *0* | *0* |
| Benign childhood epilepsy with centrotemporal spike | 8 | 9 | 0 | 0 |
| Childhood epilepsy with occipital paroxysms | 1 | 0 | 0 | 0 |
| Panayiotopoulos syndrome | 0 | 1 | 0 | 0 |
| *Symptomatic* | *82* | *89* | *4* | *4* |
| *Cryptogenic* | *72* | *64* | *1* | *0* |
| Generalized epilepsy | 72 (27.9%) | 68 (26.4%) | 5 (50.0%) | 5 (50.0%) |
| *Idiopathic* | *15* | *16* | *1* | *1* |
| Childhood absence epilepsy | 7 | 8 | 0 | 0 |
| Juvenile absence epilepsy | 0 | 0 | 1 | 1 |
| Juvenile myoclonic epilepsy | 0 | 0 | 0 | 0 |
| Epilepsy with grand mal seizures on awakening | 1 | 0 | 0 | 0 |
| Unclassified in detail | 7 | 8 | 0 | 0 |
| *Cryptogenic or symptomatic* | *42* | *34* | *1* | *1* |
| West syndrome | 20 | 10 | 1 | 0 |
| Lennox-Gastaut syndrome | 4 | 7 | 0 | 1 |
| Epilepsy with myoclonic-astatic seizures | 0 | 0 | 0 | 0 |
| Unclassified in detail | 18 | 17 | 0 | 0 |
| *Symptomatic* | *15* | *18* | *3* | *3* |
| Early myoclonic encephalopathy | 1 | 1 | 1 | 1 |
| Others | 4 | 5 | 0 | 0 |
| Unclassified in detail | 10[a] | 12 | 2 | 2 |
| Epilepsies undetermined whether focal or generalized | 14 (5.4%) | 19 (7.4%) | 0 (0%) | 1 (10.0%) |
| Dravet syndrome | 7 | 10 | 0 | 1 |
| Epilepsy with continuous spike-waves during slow-wave sleep | 3 | 4 | 0 | 0 |
| Landau-Kleffner syndrome | 3 | 3 | 0 | 0 |
| Unclassified in detail | 1 | 2 | 0 | 0 |
| Unclassified because of lack of information | 9 (3.5%) | 8 (3.1%) | 0 (0%) | 0 (0%) |
| Total | 258 | 258 | 10 | 10 |

Epilepsy classification was performed on the clinical information on December 31, 1999. Italic values indicate summed numbers of patients in the subgroups.

[a] One of the patients who had symptomatic generalized epilepsy (SGE) on December 31, 1999, had Ohtahara syndrome and subsequent West syndrome before SGE.

the prevalence day was re-diagnosed with Dravet syndrome (DS) because of recurrent seizures that were typical of DS and because the *SCN1A* mutation was detected during follow-up. Another patient was re-diagnosed with epilepsy but it was undetermined whether it was focal or generalized because she had only partial seizures by the prevalence day and she had generalized seizures including atypical absences and tonic seizures afterward. Another patient was initially diagnosed with SLRE because of early slow language development, but he was re-diagnosed with benign childhood epilepsy with centrotemporal spike (BECTS) and he developed normally during the follow-up period.

Of the 72 patients with a diagnosis of cryptogenic localization-related epilepsy (CLRE) on the prevalence day, five were re-diagnosed with SLRE including two in whom hippocampal sclerosis (mesial temporal lobe epilepsy) was detected and three in whom FCD was detected by follow-up MRI each in the temporal, parietal and occipital lobes. Another two patients were re-diagnosed with DS: one re-diagnosis was similar to the above patient with an initial diagnosis of SLRE, and the other had atypical DS, which was diagnosed by the detection of an *SCN1A* mutation. Another patient with an initial diagnosis of CLRE who had two generalized convulsive seizures with rolandic spikes on interictal EEG before the prevalence day was re-diagnosed with childhood absence epilepsy (CAE) because of the occurrence of absence seizures with typical 3-Hz diffuse spike-wave bursts on subsequent EEG.

Of the 20 patients with an initial diagnosis of WS, 10 patients remained with this diagnosis because of seizure-freedom during the follow-up period, and epilepsy evolved to SLRE in seven patients, to LGS in one patient and to other types of symptomatic generalized epilepsy (SGE) in two patients. One patient with cryptogenic or symptomatic generalized epilepsy and another lacking detailed information on the prevalence day were re-diagnosed with SGE and LGS, respectively, during the follow-up. One patient initially had Ohtahara

Table 2
Underlying diseases and specific diagnoses.

| Etiology | Group 1 ($n = 258$) | | Group 2 ($n = 10$) | |
|---|---|---|---|---|
| | December 31, 1999 | December 31, 2009 | December 31, 1999 | December 31, 2009 |
| *Perinatal complications* | *28* | *28* | *1* | *1* |
| Neonatal asphyxia | 18 | 18 | 1 | 1 |
| Premature birth | 6 | 6 | 0 | 0 |
| Neonatal hypoglycemia | 2 | 2 | 0 | 0 |
| Periventricular leukomalacia | 2 | 2 | 0 | 0 |
| *Cerebral dysgenesis/tumor* | *16* | *20* | *0* | *0* |
| Cortical dysplasia | 1 | 4 | 0 | 0 |
| Hemimegalencephaly | 3 | 3 | 0 | 0 |
| FCMD | 3 | 3 | 0 | 0 |
| Congenital CMV | 2 | 2 | 0 | 0 |
| Polymicrogyria | 2 | 2 | 0 | 0 |
| Porencephaly | 1 | 1 | 0 | 0 |
| Lissencephaly | 1 | 1 | 0 | 0 |
| Aicardi | 1 | 1 | 0 | 0 |
| Agenesis of the corpus callosum | 1 | 1 | 0 | 0 |
| Atrophy of hemisphere | 1 | 1 | 0 | 0 |
| DNT | 0 | 1 | 0 | 0 |
| *Neurocutaneous syndrome* | *10* | *10* | *2* | *2* |
| Tuberous sclerosis | 7 | 7 | 1 | 1 |
| Sturge-Weber syndrome | 1 | 1 | 0 | 0 |
| Ito-hypomelanosis | 1 | 1 | 0 | 0 |
| Nevoid-basal cell carcinoma syndrome | 1 | 1 | 0 | 0 |
| Congenital ichthyosis | 0 | 0 | 1 | 1 |
| *Cerebrovascular disorder* | *9* | *9* | *0* | *0* |
| Sequel of intracranial hemorrhage | 3 | 3 | 0 | 0 |
| Sequel of subdural hematoma | 2 | 2 | 0 | 0 |
| Sequel of infarction | 2 | 2 | 0 | 0 |
| Cavernous hemangioma | 1 | 1 | 0 | 0 |
| Moyamoya-disease | 1 | 1 | 0 | 0 |
| *Genetic neurologic disease* | *8* | *8* | *1* | *1* |
| Angelman syndrome | 4 | 4 | 0 | 0 |
| Down syndrome | 1 | 1 | 1 | 1 |
| 4p-syndrome | 1 | 1 | 0 | 0 |
| 14p+ | 1 | 1 | 0 | 0 |
| Fragile X syndrome | 1 | 1 | 0 | 0 |
| *Infection* | *6* | *5* | *1* | *1* |
| Encephalopathy/encephalitis | 4 | 3 | 1 | 1 |
| Meningitis | 2 | 2 | 0 | 0 |
| *Hypoxic-ischemic encephalopathy* | *5* | *5* | *0* | *0* |
| Post heart operation | 3 | 3 | 0 | 0 |
| Near-drowning | 2 | 2 | 0 | 0 |
| *Progressive degenerative disease* | *1* | *1* | *2* | *2* |
| Leukodystrophy | 1 | 1 | 0 | 0 |
| Hunter syndrome | 0 | 0 | 1 | 1 |
| Niemann-Pick disease | 0 | 0 | 1 | 1 |
| *Particular type of epilepsy* | *7* | *13* | *0* | *1* |
| Dravet syndrome | 7 | 10 | 0 | 1 |
| Mesial temporal lobe epilepsy | 0 | 3 | 0 | 0 |
| *Unknown except for genetic factors* | *56* | *54* | *1* | *1* |
| *Unknown* | *112* | *105* | *2* | *1* |

Italic values indicate summed numbers of patients in the subgroups. FCMD, Fukuyama type congenital muscular dystrophy.
CMV, cytomegalus virus.
DNT, dysembryoplastic neuroepithelial tumor.

syndrome during early infancy, and his epilepsy evolved to WS, and then to SGE by December 31, 1999.

For seizure frequency, 30 patients had been completely seizure free for at least 5 years before December

Table 3
Changes in epilepsy classifications during follow-up.

| Group 1 ($n = 258$) | | | |
|---|---|---|---|
| December 31, 1999 | | December 31, 2009 | |
| Idiopathic localization-related epilepsy | 1 | Panayiotopoulos syndrome | 1 |
| Symptomatic localization-related epilepsy | 5 | Lennox-Gastaut syndrome | 1 |
| | | Epilepsy with continuous spike-waves during slow-wave sleep | 1 |
| | | Dravet syndrome | 1 |
| | | Epilepsies undetermined whether focal or generalized | 1 |
| | | Benign childhood epilepsy with centrotemporal spike | 1 |
| Cryptogenic localization-related epilepsy | 8 | Symptomatic localization-related epilepsy | 5 |
| | | Dravet syndrome | 2 |
| | | Childhood absence epilepsy | 1 |
| West syndrome | 10 | Symptomatic localization-related epilepsy | 7 |
| | | Lennox-Gastaut syndrome | 1 |
| | | Symptomatic generalized epilepsy others | 1 |
| | | Symptomatic generalized epilepsy unclassified | 1 |
| Cryptogenic or symptomatic generalized epilepsy unclassified | 1 | Symptomatic generalized epilepsy unclassified | 1 |
| Lack of information | 1 | Lennox-Gastaut syndrome | 1 |
| Group 2 ($n = 10$) | | | |
| December 31, 1999 | | Last follow up | |
| Cryptogenic localization-related epilepsy | 1 | Dravet syndrome | 1 |
| West syndrome | 1 | Lennox-Gastaut syndrome | 1 |

31, 1999. On December 31, 2009, the number of patients with seizure-freedom for more than 5 years had increased to 153. In contrast, the number of patients with daily and weekly seizures slightly decreased from 38 and 13, respectively, to 28 and 10, respectively. These changes during the 10-year follow-up period were statistically significant ($p < 0.001$) (Table 4).

Regarding disability in 1999, 139 patients had no disability, 47 had only intellectual disability, one had only motor disability, and the remaining 71 had both intellectual and motor disabilities. On December 31, 2009, the number of patients with no disability decreased to 126, and the number of patients with both intellectual and motor disability increased to 75. There were 55 and two patients with only an intellectual disability and only a motor disability, respectively (Table 4).

Treatment of patients was assessed, and there were 37 patients who were not taking AED medications on December 31, 1999, and this increased to 120 on December 31, 2009. However, the number of patients taking two or more AEDs increased from 90 to 103 during the 10-year follow-up period. These changes were statistically significant ($p = 0.047$). Two patients had surgical treatment during the follow-up period. These patients both underwent surgery to remove FCD and hemispherotomy for a hemimegalencephaly. No patients underwent ketogenic diet treatment during the follow-up.

### 3.2. Group 2 dead patients

Ten patients (six males and four females) died during the follow-up period, as indicated in Table 5. Their mean age at the onset of epilepsy was exactly 2 years (median, 6 months; range, 1 day–10 years and 7 months), and seven of these patients developed epilepsy before 12 months of age. Age at death ranged from 4 to 19 years, with a mean of 13 years and 3 months.

For epilepsy diagnoses, four patients had SLRE, two had SGE and the remaining patients had DS, early myoclonic encephalopathy (EME), LGS or juvenile absence epilepsy (JAE). Eight patients had severe underlying disease, and seven of them had both intellectual and motor disabilities and the other had only an intellectual disability.

At the time of death, seizures were not controlled in six patients (seizure frequency was yearly in one, weekly in two and daily in three patients), while three patients were completely seizure-free for more than one year. The cause of death was drowning, which was possibly related to seizures in one patient (patient 9, Table 5). The cause of death seemed to be unrelated to seizures in five patients (influenza encephalopathy, tracheal bleeding, pneumonia and heart failure, bleeding from renal angiomyolipoma, and aspiration pneumonia), and it was unknown for the remaining four patients. Patient 9 with JAE had no underlying disease or disability. She had been diagnosed with JAE and had absence seizures at least once per week at the time of her death, but she died suddenly immediately after a generalized seizure at 19 years of age.

### 3.3. Group of patients lost to follow-up

Of the remaining 82 patients who were lost to follow-up during the 10-year period, we obtained information

Table 4
Seizure frequency, additional disability and antiepileptic medication.

| | | Group 1 ($n = 258$) | | Group 2 ($n = 10$) | |
|---|---|---|---|---|---|
| | | 1999 | 2009 | 1999 | Last |
| Frequency of seizure[a] | No seizure ⩾ 5 years [1] | 30 | 153 | 1 | 3 |
| | No seizure for >1 year and <5 years [2] | 90 | 32 | 3 | 0 |
| | Yearly [3] | 69 | 17 | 3 | 1 |
| | Monthly [4] | 18 | 18 | 1 | 0 |
| | Weekly [5] | 13 | 10 | 0 | 2 |
| | Daily [6] | 38 | 28 | 2 | 4 |
| Disability | None | 139 | 126 | 1 | 1 |
| | Intellectual & motor | 71 | 75 | 8 | 8 |
| | Intellectual only | 47 | 55 | 1 | 1 |
| | Motor only | 1 | 2 | 0 | 0 |
| The number of AEDs[b] | 0 [1] | 37 | 120 | 0 | 0 |
| | 1 [2] | 128 | 35 | 4 | 3 |
| | 2 [3] | 46 | 44 | 3 | 1 |
| | 3 [4] | 35 | 28 | 3 | 5 |
| | ⩾4 [5] | 9 | 31 | 0 | 1 |
| | Unidentified | 3 | 0 | 0 | 0 |

AEDs, antiepileptic drugs; [], rank index for statistical analysis.
Changes of rank indices in Group 1 during the 10-year follow-up period were statistically significant with $p < 0.001$[a] and $p = 0.047$[b] using the Wilcoxon signed-rank test.

regarding the changes of epilepsy classification in six of these patients: in two with an initial diagnosis of West syndromes, epilepsy in each evolved to SLRE and LGS, and four with initial CLRE were re-diagnosed with PS based on the latest epilepsy classification.

## 4. Discussion

Our objective was to clarify the long-term clinical course of childhood epilepsy during a period of 10 years, using data that followed an epidemiological study in the restricted area of Okayama Prefecture, Japan [7]. The investigation into changes in the epilepsy diagnosis and classification in the present study, from an epidemiological point of view, is important because other studies on changes in the epilepsy classification were largely limited to certain epilepsy syndromes such as West syndrome and IGE [18–21]. There are still few comprehensive long-term epidemiological studies on such changes [14,15]. In addition, we could follow marginal patients who had experienced only acute symptomatic seizures or single unprovoked seizures with epileptiform abnormalities on the EEG at the time of initial prevalence day: we could assess this group of patients because almost all subjects had undergone EEG recordings.

In the 258 patients in the present study, onset age of epilepsy tended to be young, with an average of 3.0 years because of the presence of more children with infantile onset epilepsies (87 patients; 33.7%) such as West syndrome (20 patients; 7.8%) and DS (10 patients; 3.9%) than other studies, where the proportion of patients with these syndromes was <3% [1,4–6,22]. Age at onset of epilepsy was highest within the first year of life (87 patients; 33.7%). There was a relatively high rate of patients with intractable epilepsy and the number of the patients with at least yearly seizures in 1999 was 138 of 258 (53.5%) in the present study, compared to 681 of 2,220 (30.7%) in the previous study [7].

### 4.1. Etiology

In the 258 patients in the present study, etiologies were identified in 99 patients (38.4%) at their final follow-up. This percentage was similar to those in other reports [1–4,8]. The identification of etiologies was performed during the follow-up period in nine patients, and three patients had *SCN1A* mutations, three had FCD, two had hippocampal sclerosis, and one had DNT. Of the 159 patients with epilepsy of unknown cause, 18 met the criteria for specific epileptic syndromes including BECTS, PS and CAE. There were 54 patients (20.9%) who had a family history of seizure disorders.

### 4.2. Seizure outcome and treatment

The number of patients with no seizures for at least 5 years markedly increased from 30 in 1999 to 153 in 2009, but the rate of seizure-free patients (153/258 or 59.3%) was somewhat low compared to the rates from other studies, which averaged around 65% (range, 51–76%) [8,10,12–14,21,23,24]. This may be because there was a high percentage of patients with refractory epilepsy who continued to be treated at Okayama University Hospital, a tertiary epilepsy center. The number of

Table 5
Mortality during follow-up.

| | Sex | Classification | Underlying disease | Disability | Seizure onset | Age at death | Frequency of seizure | Cause |
|---|---|---|---|---|---|---|---|---|
| 1 | M | Dravet syndrome | *SCN1A* mutation | Intellectual & motor | 3 m | 4 y 4 m | Weekly | Influenza encephalopathy |
| 2 | M | SGE | Hunter syndrome | Intellectual & motor | 2 y 2 m | 5 y 6 m | Daily | Tracheal bleeding |
| 3 | M | SLRE | Unidentified | Intellectual & motor | 1 day | 11 y 2 m | Yearly | Drowning |
| 4 | M | SLRE | Niemann-Pick disease | Intellectual & motor | 4 y 10 m | 13 y 2 m | Unknown | Pneumonia & heart failure |
| 5 | F | SLRE | Tuberous sclerosis | Intellectual | 4 m | 14 y 0 m | No seizures | AML bleeding |
| 6 | M | EME | Meningoencephalitis | Intellectual & motor | 3 m | 14 y 11 m | Daily | Unknown |
| 7 | F | SLRE | Neonatal asphyxia | Intellectual & motor | 11 m | 15 y 0 m | No seizures | Unknown |
| 8 | M | LGS | Down syndrome | Intellectual & motor | 5 m | 15 y 10 m | Daily | Unknown |
| 9 | F | JAE | Unidentified[a] | None | 10 y 7 m | 19 y 4 m | Weekly | Unknown |
| 10 | F | SGE | Congenital ichthyosis | Intellectual & motor | 7 m | 19 y 5 m | No seizures | Aspiration pneumonia |

SGE, symptomatic generalized epilepsy.
SLRE, symptomatic localization-related epilepsy.
EME, early myoclonic encephalopathy.
LGS, Lennox-Gastaut syndrome.
JAE, juvenile absence epilepsy.
AML, renal angiomyolipoma.
[a] Family history of seizure disorders.

patients who had seizures at least monthly only slightly decreased from 69 in 1999 to 56 in 2009, suggesting that patients with frequent seizures remained resistant to treatment even for a decade.

For treatment, though the number of AEDs generally decreased, antiepileptic medication was continuing in 138 patients (53.5%) at the final follow-up. This rate was higher than previously-reported rates of around 35% [11,23]. This may be because of the high proportion of intractable patients.

### 4.3. Neurological disabilities

In the 258 patients, a total of 130 (50.4%) and 77 (29.8%) patients had an intellectual disability and a motor disability, respectively, on December 31, 2009, including 75 (29.1%) with both disabilities. In previous reports, the rate of patients with the comorbidity of epilepsy ranged from 24% to 39% for intellectual disability [2,3,5,6,8,22] and from 16% to 46% for motor disability [2,3,5,6,22]. The results of the present study were similar to those in previous studies [2,6,22].

### 4.4. Changes in epilepsy diagnosis

Epilepsy classification was changed in 26 (10.1%) of 258 patients during the decade-long follow-up. In addition, the epilepsy classification was changed during the follow-up for two dead patients and six of the 82 patients lost to follow-up. The reasons for these changes include: (1) the recognition of new epileptic syndrome such as PS; (2) age-dependent evolution of epileptic syndromes; (3) detection of underlying pathology particularly malformation of cortical development by advances of neuroimaging techniques; and (4) identification of genetic abnormalities associated with epilepsy. In previous studies, epilepsy classification was changed in 7–33% of patients during follow-up [14,15,18–21]. Therefore, changes in the epilepsy classification are common, and could be determined by careful observation over a long period in the present study.

Summarizing the changes in epilepsy classification in all patients in the present study, five patients were re-diagnosed with PS, a newly recognized syndrome, during follow-up. Evolution of epileptic syndromes occurred in 15 patients. Thirteen patients had symptoms that evolved, as follows: from West syndrome to SLRE in eight; LGS in three and SGE in the remaining two. Another patient showed an evolution from SLRE to ECSWS. The remaining patient initially had West syndrome and her epilepsy evolved to SLRE before 1999, and then to LGS before 2009. West syndrome often evolves to other disorders such as related-localization epilepsy, LGS and other types of generalized epilepsy. Ohtahara et al. reported that 51 of 94 patients with West syndrome evolved to LGS [18]. Camfield et al. reported

that in 32 patients with an initial diagnosis of West syndrome, the diagnosis changed to partial epilepsy in four, to LGS in 11, and to unspecified SGE in nine, and that it did not change in the remaining eight [20]. In the present study, five patients who had been initially diagnosed with CLRE were re-diagnosed with SLRE during follow-up because of pathology detected by MRI.

Genetic examination is helpful to identify the cause of epilepsy, which was unavailable for a long time, particularly in DS that has a mutation in the *SCN1A* gene. In the present study, the diagnosis of DS was established in four patients by detection of *SCN1A* mutations during the follow-up period. Two of these patients were less than 18 months of age and had not yet shown all the characteristics of DS on the prevalence day in 1999. The other two patients had atypical DS because of an inconspicuous intellectual disturbance on the initial prevalence day.

We expect that more patients may be re-diagnosed as there are further technical advances in neuroimaging and genetic examination. For a precise epidemiological study of epilepsy classification, a long-term follow-up study is required.

### 4.5. Mortality

Of 10 patients who died in Group 2, nine had symptomatic epilepsy, particularly severe underlying disorders and seven developed epilepsy during the first year of life. It was, therefore, suggested that the presence of underlying disorders, neuro-deficits including intellectual disability, and early onset of epilepsy are among the risk factors for death, which is consistent with previous reports [8–10,20,23–27]. Sillanpää et al. reported that the mortality in epilepsy patients is three times as high as the mortality in the general population and that symptomatic causes and severe cognitive impairment are among the risk factors for death [24]. They also indicated that deaths in childhood occurred primarily in the symptomatic group and were most often not related to epilepsy but to the underlying diseases. Moseley et al. suggested that children with epilepsy onset in the first year of life were over six times more likely to die than children with later onset epilepsy [27]. We confirmed their observations in the present study.

Conversely, a 19-year-old patient (patient 9 in Table 5) with JAE suddenly died immediately after a generalized seizure. Although the previous reports indicated that incidence of sudden unexpected death in epilepsy (SUDEP) and mortality of the patients with uncomplicated epilepsy is not higher than the general population [9,25,26,28,29], Sillanpää et al. reported a similar patient with JAE who suddenly died, probably as a result of a brief unwitnessed seizure, and indicated that almost all the mortality in the idiopathic/cryptogenic group occurred in adult life [30].

### 4.6. Limitations of the study

There were a few limitations in the present study. The first limitation was a high proportion of patients whose information was unavailable: patients who did not visit Okayama University Hospital could not be located. The second limitation is a subject bias. Because Okayama University Hospital is a tertiary epilepsy center for patients with intractable epilepsy, the proportion of patient with refractory epilepsy was higher than that of previous studies.

### 4.7. Conclusions

We comprehensively investigated the changes in epilepsy diagnosis over a decade. This 10–year-long follow-up was longer than most of the previous reports and disclosed detailed clinical characteristics of childhood epilepsy. Etiologies of currently-unknown causes may be identified in more patients via further advancements in neuroimaging and genetic examination. To clarify all the chronic aspects of epilepsy including seizure outcome, social issues and mortality, life-long follow-up involving a larger sample of patients may be needed.

## Disclosure

None of the authors have any conflicts of interest to disclose.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.braindev.2016.10.011.

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