Management of Childhood-onset Epilepsy
Evaluated with a Long-term Follow-up Study

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Abstract

Purpose: While many patients with childhood-onset epilepsy go into remission before reaching adulthood, a significant number of patients continue to suffer from refractory epilepsy. The purpose of this study was to clarify the long-term outcome of childhood-onset epilepsies.

Subjects and Methods: We retrospectively studied 445 adult patients with childhood-onset epilepsies who were still being treated at the Department of Child Neurology, Okayama University Hospital.

Results: Age at onset of epilepsy was < 7 years in 66% of the patients; 7 to 14 years in 30%; and 15 to 19 years in 5%. We classified the subjects into three groups: Group PE (289 patients) with partial epilepsy; Group GE (60 patients) with generalized epilepsy; Group RE (70 patients) consisting of patients with a history of West syndrome, Lennox-Gastaut syndrome, Doose syndrome and related epileptic syndromes; and 26 other unclassified cases. At follow-up, frequent seizures (≥1 per month) were observed in 26%, 13% and 63% of patients in Groups PE, GE and RE, respectively. Of 168 patients in remission across these three groups, AEDs were discontinued or being reduced in 21% each, while 36% had experienced relapse of seizures, mainly caused by AED withdrawal.
Discussion: This study indicated that these adult patients could be classified into two types: patients who still have frequent seizures even after reaching adulthood, and patients in remission or with rare seizures. For long-term management of these patients, an efficient system with cooperation between medical and comedical staff, and a comprehensive care system are essential.

Introduction

Many patients with childhood-onset epilepsy have benign epilepsies, but there are also a significant number of adult patients with refractory epileptic syndromes that began in childhood. Childhood-onset epilepsy is diagnosed by pediatric neurologists; when patients reach adulthood, a significant number continue to be treated by the same pediatric neurologists, although some are referred to other doctors who specialize in adult epilepsy. Epilepsy is a common chronic neurological disorder, therefore management of childhood-onset epilepsy requires a long-term perspective.

In this article we present data on adult patients with childhood-onset epilepsy whom we are still treating, and discuss the problems related to the management of these patients from various perspectives.

Subjects and Methods

It would have been technically difficult to extract all the data of the patients with epilepsy that we regularly treat from the database of Okayama University Hospital. On the other hand, in the Department of Child Neurology, Okayama University Hospital, we have an EEG database. Our patients basically undergo at least one EEG every year during the follow-up period. Therefore, we reviewed the EEG database of our department from January 1, 2004 to December 31, 2005, and selected all patients with epilepsy who were 20 years of age or older on December 31, 2003. Then we reviewed the medical records of these candidate cases.

The patients who met our selection criteria for this study consisted of 445 adult patients (235 males and 210 females) whose seizures started during childhood (<20 years) and who were still being treated at the Department of Child Neurology, Okayama University Hospital as of December 31, 2003, which we set as the surveillance day. We performed a retrospective review of their medical records, and investigated their clinical data such as age at time of survey, age at onset of epilepsy, seizure frequency at time of survey, epilepsy classification and evolulutional changes, and the problems experienced by patients in remission. Remission was defined as freedom from seizures for three years or longer at the time of survey. As for seizure frequency, “daily occurrence” was defined as ≥1 per day, “weekly occurrence” as ≥1 per week, “monthly occurrence” as ≥1 per month, and “yearly occurrence” as <1 per month or freedom from seizures for <3 years.

Results

The age distribution at the time of survey was
as follows: 256 (58%) were in their twenties, 135 (30%) in their thirties, 44 (10%) in their forties, and the other 10 (2%) were 50 years or older (Figure 1-A).

Seizures started at 6 years or younger in 292 (66%) of the 445 patients, at 7 to 14 years in 132 (30%), and at 15 to 19 years in 21 (5%) (Figure 1-B).

As for classification of epilepsy, 289 patients suffered from partial epilepsy throughout their clinical course (Group PE). Another 60 patients had generalized epilepsy (Group GE). The third group (Group RE) consisted of 70 patients with a history of West syndrome, Lennox-Gastaut syndrome, Doose syndrome and related epileptic syndromes. The patients in this group had refractory generalized epilepsies in the early period. The remaining 26 patients did not fit into any of these groups: 10 patients with severe myoclonic epilepsy in infancy, 10 patients with epilepsy with continuous spike-waves during slow-wave sleep, and 6 patients with other unclassified epilepsy.

The distribution of seizure frequency at the time of survey in all 445 subjects was as follows: 182 patients (41%) were in remission; yearly occurrence was observed in 128 (29%); and frequent seizures, including daily (48 patients), weekly (22 patients), and monthly occurrence (65 patients) were seen in a total of 135 (30%) patients. We focused on 419 patients in Groups PE, GE and RE. Comparing seizure frequency among these three groups, seizure outcome was the best in Group GE and worst in Group RE (Table 1).

Among the patients in Group RE, epilepsy always started as refractory generalized epilepsy, such as West syndrome or Lennox-Gastaut syndrome. At the time of survey, however, their clinical features had changed significantly since childhood. In many of these patients, epilepsy started as Lennox-Gastaut syndrome or West syndrome and underwent evolitional change to severe epilepsy with multiple independent spike foci (SE-MISF) (1, 2, 3) or partial epilepsy.

We now present a representative case of SE-MISF. This patient suffered from Lennox-Gastaut syndrome since he was one year of age after suffering from encephalitis. When he was younger, his EEGs showed diffuse slow
spike-waves. However, his EEGs gradually lost the characteristics of Lennox-Gastaut syndrome, and began to display multifocal spikes as shown in Figure 2. His seizure types, namely tonic spasms and tonic seizures, did not change during the clinical course. We diagnosed him as having SE-MISF at the time of survey. Figure 3 shows an ictal EEG of this patient during a tonic seizure. Diffuse fast activity suddenly appeared without lead-in in

Table 1: Seizure frequency at time of survey

<table>
<thead>
<tr>
<th>Frequent seizures</th>
<th>Yearly occurrence</th>
<th>Remitted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group PE</td>
<td>75 (26%)</td>
<td>99 (34%)</td>
</tr>
<tr>
<td>Group GE</td>
<td>8 (13%)</td>
<td>17 (28%)</td>
</tr>
<tr>
<td>Group RE</td>
<td>44 (63%)</td>
<td>8 (11%)</td>
</tr>
<tr>
<td>Total</td>
<td>127 (39%)</td>
<td>124 (39%)</td>
</tr>
</tbody>
</table>

Frequent seizures: seizures occurring ≥1 per month. Yearly occurrence: <1 per month or freedom from seizures for <3 years.

Table 2: Patients in seizure remission at time of survey: use of AEDs

<table>
<thead>
<tr>
<th>Remitted cases</th>
<th>No AEDs</th>
<th>Reduction of AEDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group PE</td>
<td>115</td>
<td>25 (22%)</td>
</tr>
<tr>
<td>Group GE</td>
<td>35</td>
<td>7 (20%)</td>
</tr>
<tr>
<td>Group RE</td>
<td>18</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>Total</td>
<td>168</td>
<td>36 (21%)</td>
</tr>
</tbody>
</table>

Table 3: Patients in seizure remission at time of survey and relapse during clinical course

<table>
<thead>
<tr>
<th>Remitted cases</th>
<th>Relapse during clinical course</th>
<th>Relapse related with AEDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group PE</td>
<td>115</td>
<td>44 (38%)</td>
</tr>
<tr>
<td>Group GE</td>
<td>35</td>
<td>13 (37%)</td>
</tr>
<tr>
<td>Group RE</td>
<td>18</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>Total</td>
<td>168</td>
<td>60 (36%)</td>
</tr>
</tbody>
</table>

Table 4: Patients in seizure remission at time of survey but without AED reduction

<table>
<thead>
<tr>
<th></th>
<th>Cases without AED withdrawal</th>
<th>Spikes on recent EEGs</th>
<th>Relapse during clinical course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group PE</td>
<td>62</td>
<td>26 (42%)</td>
<td>35 (58%)</td>
</tr>
<tr>
<td>Group GE</td>
<td>25</td>
<td>14 (56%)</td>
<td>10 (40%)</td>
</tr>
<tr>
<td>Group RE</td>
<td>0</td>
<td>4 (44%)</td>
<td>2 (22%)</td>
</tr>
<tr>
<td>Total</td>
<td>96</td>
<td>44 (46%)</td>
<td>47 (49%)</td>
</tr>
</tbody>
</table>
**Figure 2** An interictal EEG during sleep of a 22-year-old patient with severe epilepsy with multiple independent spike foci. Calibration: 50 μV, 1 sec.

**Figure 3** An ictal EEG of a tonic seizure in the same patient at the age of 23 years. Calibration: 50 μV, 1 sec.
any region.

The patients in remission accounted for 182 (41%) of all 445 subjects. We focused on 419 patients in Groups PE, GE and RE. The patients in remission in these three groups comprised 115 (40%) in Group PE, 35 (58%) in Group GE, and 18 (26%) in Group RE (Table 1). Among the 168 patients in remission in these three groups, 21% of patients were off medication, and in another 21% antiepileptic drugs (AEDs) were being reduced at the time of survey (Table 2). The remaining 58% were on AEDs without reduction. Relapse during the clinical course was observed in 60 (36%) of 168 patients in remission, and relapse was related to intentional withdrawal of AEDs in 56 out of the 60 patients (Table 3). Among the patients in remission but without AED reduction at the time of survey, 46% of patients had spikes in their most recent EEGs. Nearly half of the patients had experienced seizure relapse during the clinical course (Table 4).

Discussion

According to existing long-term follow-up studies of childhood-onset epilepsies, it is thought that most patients eventually have favorable outcome (4, 5, 6). However, the detailed long-term clinical course of refractory patients with childhood-onset epilepsies has not yet been fully elucidated (7, 8). Epilepsies that began as refractory childhood epilepsy syndromes such as West syndrome and Lennox-Gastaut syndrome often undergo evolutionary change (9, 10, 11), but long-term follow-up studies of these cases are scarce (12).

In addition, the long-term outcome of patients who enter remission at one point during childhood is not clear (13). Sillanpää and Schmidt (13) reported the natural history of treated childhood-onset epilepsy in a prospective, long-term population-based study. They followed 144 patients for an average of 37.0 years from the time of the first seizure which occurred before the age of 16 years. They concluded that half of the patients with childhood-onset epilepsy would eventually enter terminal remission (freedom from seizures for five years or more at the end of follow-up) without relapse and a fifth would enter terminal remission after relapse, while a third would have a poor long-term outcome of persistent seizures relapsing after remission or without any remission ever. These findings suggest that a significant number of patients with childhood-onset epilepsy have a remitting-relapsing pattern during their clinical course, and need long-term management.

Although our study is a retrospective hospital-based study, it indicates that a significant number of patients with childhood-onset epilepsy were still being treated in our Department of Child Neurology after reaching adulthood. The adult patients we presented in this article account for roughly one-third of all patients with epilepsy regularly seen in our department. Since our department has been specialized in epilepsy for many years, we may be in a special situation, but we almost always continue to treat patients even after they reach adulthood. When they have some associated symptoms such as psychiatric symptoms and psychosocial problems, we
consult specialists, and treat the patients in cooperation with these specialists. Whenever patients want to move to the psychiatry or adult neurology departments, we refer them, but those are exceptional cases. To date these carry-over cases have not been fully investigated, but we suspect that many hospitals and clinics in Japan that deal with patients with childhood-onset epilepsy share the same difficulties we have experienced in handling carry-over cases. In order to achieve successful long-term management of patients with childhood-onset epilepsy, cooperation among pediatric neurologists and pediatricians, adult neurologists, psychiatrists, other medical staff, and in some cases neurosurgeons is inevitable. Yet in Japan, at least, there are few efficient systems or networks in place to care for patients with epilepsy throughout their lives.

Through this investigation we identified two groups of patients who often lack the services they need (Figure 4). One group consists of patients who have frequent seizures even after reaching adulthood, and the other group consists of those in remission or having rare seizures. The former group of patients is most often seen in Group RE, but there are also a significant number of patients in Group PE who experience frequent seizures. For these refractory cases, therapy with novel AEDs are definitely necessary (14) especially in Japan, since many AEDs used in other countries have never been available in Japan. Alternatively, some of these cases can be successfully treated by epilepsy surgery, especially cases in Group PE (15, 16). We must search extensively for candidates for epilepsy surgery as early in the patients’ lives as possible.

The other group that comprises patients with rare seizures and those in remission but still on AEDs has received insufficient attention to date because of a lack of long-term follow-up studies throughout their lives (13). It is well known that seizures tend to recur after reduction of AEDs, especially in idio-

Figure 4 Long-term clinical course and management issues of patients with childhood-onset epilepsy
pathic generalized epilepsies treated with VPA. In our present study, however, almost the same percentage of patients in Group PE and Group GE had relapse. As for suspected causes, relapse often occurred in relation to intentional withdrawal of AEDs. A significant number of patients in remission who were still on AEDs had epileptic discharges and/or experience of relapse during their clinical course. These facts suggest that patients who were apparently in remission at the time of our survey may include those who still have active epileptic mechanisms. In general, seizure outcome after stopping AEDs is favorable, especially in children (17, 18). However, a small number of patients do not enter remission again despite treatment for relapse following a planned discontinuation of AEDs (19, 20). Adult patients in remission or with rare seizures have jobs and families, and many of them have a driver’s license. Naturally, patients and their doctors hesitate to reduce AEDs in patients who have already experienced relapse. On the other hand, a study on the quality of life of adults with childhood-onset epilepsy (21) reported a persistent long-term adverse impact on health-related quality of life, and the major impact was on those still on medication as adults. Clearly, decisions about when or how to stop medication are complicated, and vary depending on the situation of each patient.

Since this is not a prospective study, we have not been able to track the exact clinical course of all patients who have ever visited our department. Thus, we must acknowledge that the present study covers only a limited selection of childhood-onset epilepsy cases; there must have been many patients who entered remission during childhood and consequently dropped out from our follow-up system before reaching adulthood (Figure 4). In addition, we do not know the exact number of disabled patients with refractory seizures who were institutionalized during childhood, and dropped out from our follow-up system because they were being treated in these institutions. To further elucidate the long-term outcome of childhood-onset epilepsy, a prospective longitudinal follow-up study of all patients from their first visit is needed, but this kind of long-term study is technically difficult to perform. Therefore, the data from our present study will be useful in planning treatment strategies for various types of childhood-onset epilepsy.

References
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