Early seizure frequency and aetiology predict long-term medical outcome in childhood-onset epilepsy

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In clinical practice, it is important to predict as soon as possible after diagnosis and starting treatment, which children are destined to develop medically intractable seizures and be at risk of increased mortality. In this study, we determined factors predictive of long-term seizure and mortality outcome in a population-based cohort of 102 children. At the end of the 40-year median follow-up, since their first seizure before the age of 16 years, 95 (93%) of 102 patients had entered one or more one-year remissions (1YR). In contrast, 7 (7%) patients never experienced any 1YR and their epilepsy was considered drug-resistant. Two factors present early in the course of treatment were found to be associated with adverse outcome. Having weekly seizures during the first year of treatment carried an 8-fold risk [hazard ratio 8.2 (1.6–43.0), P = 0.0125] of developing drug resistant epilepsy and a 2-fold risk of never entering terminal 1YR [hazard ratio 2.7 (1.5–5.0), P = 0.0010]. Having weekly seizures prior to treatment only slightly increased the risk to never enter terminal 1YR [hazard ratio 1.7 (1.04–2.9), P = 0.0350]. Thirteen of 102 patients (13%) died during follow-up. Long-term mortality was 9-fold higher for patients with symptomatic epilepsy [hazard ratio 9.0 (1.8–44.8), P = 0.0071]. Mortality was not, however, increased by having weekly seizures prior to or during the first year of treatment versus fewer seizures. Early seizure frequency can predict long-term seizure control during antiepileptic drug treatment, but not mortality. Aetiology, however, is predictive of both seizure outcome and mortality in childhood-onset epilepsy. Using these criteria allows early identification of children destined to develop intractable epilepsy and increased mortality.

Keywords: epileptology; epilepsy prognosis; childhood; seizures; mortality

Abbreviations: AEDs = antiepileptic drugs; GTC = generalized tonic–clonic seizures; 1YR = one-year remission

Introduction

It is well known that as many as two of three newly treated patients with epilepsy will eventually enter long-term remission for several years (Annegers et al., 1979; Cockerell et al., 1995; Camfield and Camfield, 2003; Sillanpää and Schmidt, 2006). However, there is an uncertainty which features, present at the first year of treatment, if any, predict poor long-term outcome and mortality in new-onset childhood epilepsy (Camfield and Camfield, 2003). In clinical practice, it is important to predict...
within a year after diagnosis and starting treatment the likely clinical course of childhood-onset epilepsy, both in terms of seizure control, and even more pressing, clinically relevant intractability and increased risk of death. In addition to providing parents with answers, this could allow for more aggressive treatment with modern antiepileptic drugs (AEDs) to obtain the maximal drug response to overcome drug-resistance without delay, if possible (Luciano and Shorvon, 2006; Schiller and Najjar, 2008) and, if needed, early neurosurgical intervention in suitable cases (Langfitt and Wiebe, 2008). Initial seizure frequency appeared to be a predictor for seizure control in several community- or population-based studies of childhood-onset epilepsy (Casetta et al., 1999; Berg et al., 2001). However, a community-based cohort of 77 children with new-onset temporal lobe epilepsy, who were followed prospectively with formal review seven and 14 years following seizure onset, lesions on MRI, but not initial seizure frequency or early seizure remissions, were predictive of seizure outcome (Spooner et al., 2006). In addition, frequent seizures from the onset may be the first manifestation of various epileptic syndromes with a wide range of severity, particularly in childhood (Dulac et al., 2007). Very few studies of death in epilepsy have included a substantial number of children with a long follow-up of 20 years or longer since the onset of their epilepsy (Sillanpää et al., 1995; Camfield et al., 2002). In these studies, mortality increased with time and most of the deaths were related to the presence of a severe neurological deficit, remote symptomatic aetiology or both and not directly to the seizures themselves (Sillanpää et al., 1995; Camfield et al., 2002). However, in one of the largest population-based studies of patients with remote symptomatic epilepsy, both the frequency and the type of seizures affected mortality (Strauss et al., 2003). The authors did not address cause-specific mortality rates (Strauss et al., 2003). Taken together, it is unclear if weekly seizure frequency in the first year of treatment determines mortality in childhood-onset epilepsy above the risk attributable to the underlying aetiology. The purpose of the present study was to examine which early clinical features predict seizure outcome and mortality in patients followed for several decades since the onset of their epilepsy in childhood.

Methods

Patients

The study subjects were all children under the age of 16 years at diagnosis who were living in the catchment area of University of Turku Central Hospital, Turku, Finland, at the end of 1964 and who met the criteria for epilepsy (two or more unprovoked seizures) (Commission on Classification and Terminology, 1981; Central Statistical Office of Finland, 1989; Commission on Epidemiology and Prognosis, 1993). Subjects were identified on the basis of hospital, institution and primary health care records, and a review of the National Health Service records, a registry of all patients residing in Finland. Altogether, 245 patients were identified, 223 (91%) of them were seen in the University of Turku Central Hospital. The remaining 22 patients (9%) were seen in other hospitals, institutions and public or private primary or outpatient care offices. In Finland in the 1960s, the rule was that children with an epileptic seizure were referred for evaluation. Untraceable and subsequently beyond the study remained only three more patients who, in an ongoing surveillance, were identified and who met the inclusion criteria. Thus, the patient sample represents a population-based cohort of children aged 0–15 years with epilepsy.

The 245 patients included 150 (61%) patients with incidence cases, i.e. they were first evaluated for epilepsy from 1 January 1961 to 31 December 1964, at the university hospital. The remaining 95 patients (39%) had been seen for epilepsy both before and during the study period of 1961–64. For the 95 patients seen later than the first year, which were excluded from the present study, the early seizure frequency was determined at the time of enrolment in the study. They had had at least one seizure in the preceding 3 years before the evaluation during the study period (prevalent cases). All 245 patients were examined and evaluated by one child neurologist, enrolled in a prospective follow-up of medical and social outcomes for additional 40 years. The decision to treat was made by the parents and neurologist, however, many parents were reluctant to start treatment with the then available drugs, mainly phenobarbital or phenytoin, even in the presence of weekly seizures during the first year of the epilepsy. Follow-up included ongoing review of the medical records and a comprehensive evaluation with 5-year intervals. The diagnosis of the epilepsy syndrome and the aetiology was made. Starting in 1992, in addition to the structured extensive questionnaires, the evaluation included clinical examination completed with appropriate tests for physical fitness and laboratory investigations including neuroimaging in most patients with difficult-to-treat epilepsy. The neuroimaging data will be discussed in a separate study. The study design and some earlier results have been discussed earlier (Sillanpää et al., 1998, 1999, 2004; Sillanpää and Shinnar, 2002; Sillanpää and Schmidt, 2006, 2008).

All 245 patients were under the age of 16 years at diagnosis. For the present study, 150 patients who had been followed since the onset of epilepsy under the age of 16 (incident cases) were included. Of these 150 patients, six (4%) were excluded due to <10-year follow-up, 41 for episodes of status epilepticus and one patient for self-induced photosensitive seizures. The reason to exclude patients with status epilepticus was that counting individual seizures is more difficult in status epilepticus and patients with status epilepticus may also differ in their mortality from the rest of the study population. Thus, the remaining 102 (68%) constitute the present population-based study cohort.

Definitions

Epileptic syndromes, epilepsies, epileptic seizures and aetiology of seizures were defined according to the guidelines for epidemiologic research of the International League against Epilepsy (Commission on Classification and Terminology, 1981; Central Statistical Office of Finland, 1989; Commission on Epidemiology and Prognosis, 1993). Epilepsy syndromes were grouped together for this study as generalized, temporal, extra-temporal or other (undetermined whether generalized or focal and unclassifiable). In our study, status epilepticus is defined as a seizure lasting more than 30 min or recurrent seizures lasting a total of >30 min without the patient fully regaining consciousness (Commission on Epidemiology and Prognosis, 1993; Sillanpää and Shinnar, 2002). Random generalized epilepsy was defined as epilepsy with generalized tonic–clonic seizures (GTC) randomly distributed during the sleeping–waking cycle (Janz, 1969). Remission was defined operationally as the first year that the patient was seizure-free. Terminal remission was the term used for remission at the end of follow-up. Terminal remission could be uninterrupted from the start of treatment to the end of follow-up (remitting course) or
be interrupted by relapse (remitting-relapsing course). Early uninterrupted terminal remission was defined as complete seizure freedom from the start of the first adequate therapy, not interrupted by relapse until the end of the follow-up period. Epilepsy was called drug-resistant if one-year remission (1YR) was not achieved during a follow-up of at least 10 years despite adequate treatment (Loiseau and Jallon, 1995; Picot et al., 2008). Relapse was defined as the occurrence of repeated seizures after a patient had entered remission of 1 year or more. The definition of adequate medication used for this study included early and high-dose first treatment with then standard AEDs after one or, more often, after two seizures (see Results section). Treatment was provided in accordance with contemporary practice parameters of good therapy. Compliance was determined by questioning the patient. Compliance was termed good if the patient answered: ‘Yes according to the given instructions’ to the question: ‘have you taken your drugs regularly?. The other options were: ‘Yes, regularly, but less than instructed’ ;’I have occasionally forgotten medication’; ‘I have taken the medication irregularly’; ‘There have been longer breaks in the medication’; or ‘I have spontaneously discontinued the medication’.

Sudden unexpected death (SUDEP) was defined according to Nashef (1997) as sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in an individual with epilepsy with or without evidence for a seizure and excluding documented status epilepticus where post-mortem examination does not reveal a cause of death.

Statistical analysis
For statistical analyses, Pearson’s χ² test with Fisher’s exact test (two-tail), Mann-Whitney test, Kaplan-Meier method with a log rank test and Cox proportional hazards regression were used. The Received Operating Characteristic (ROC), quantified by the Area under the Curve (AUC), was calculated from logistic regression models and was used to predict how well individual factors predict outcome. A P-value of <0.05 was considered statistically significant. Statistical computations were done using SAS System for Windows, release 9.1.3 (SAS System for windows release 9.1.3, 2003). The Joint Ethics Review Committee of the University of Turku and the University Central Hospital of Turku approved the study design.

Results
Clinical features of the patients
Table 1 summarizes the clinical features of the 102 patients of the population cohort including the aetiology of the epilepsy and the seizure frequency in the 12 months prior to and during the first year of drug treatment (Table 1).

Long-term seizure outcome
Long-term seizure outcome was assessed by the proportion of patients entering the following subgroups: 1YR ever, one-year terminal remission (1YTR) and uninterrupted 1YTR.

One-year remission ever
At the end of the 40-year follow-up (median 40.0, mean 37.6, SD 7.1, range 11–42), since their first seizure before the age of 16 years, 95 (93%) of 102 patients had entered one or more 1YR.

In contrast, 7 (7%) of patients never experienced any 1YR and their epilepsy was considered drug-resistant (Fig. 1). The follow-up of the seven patients with drug-resistant epilepsy was 24 years (median 24.0, mean 23.6, SD 12.4, range 11–41). Five out of the seven patients had generalized seizures and two focal ones of extratemporal origin. Two patients had annual, one further patient had monthly and the remaining four had weekly seizures. None of them had pretreatment clustering of seizures.

Univariate analysis (log rank test) revealed two factors that were associated with entering first 1YR: seizure frequency less than weekly versus weekly during the first year of treatment (P=0.0001) and idiopathic/cryptogenic versus symptomatic aetiology (P=0.0109). In contrast, pretreatment seizure frequency (P=0.3825), epilepsy syndrome as defined above (P=0.3397), generalized versus focal epilepsy (P=0.2563), age of onset of epilepsy (P=0.8006) and gender (P=0.9937) were not significantly associated with ever entering 1YR. In multivariate analysis (Cox proportional hazards regression), seizure frequency less than weekly versus weekly during the first year of treatment (P=0.0237, hazard ratio 1.8 (1.1–3.1)) was significantly associated with entering 1YR. Idiopathic/cryptogenic versus symptomatic aetiology of epilepsy was not significantly associated with entering 1YR (P=0.6271, log rank). AUC was 0.76 for seizure frequency during treatment, 0.69 for aetiology of epilepsy and 0.61 for pretreatment seizure frequency.

Univariate analysis (log rank test) revealed two factors that were associated with entering uninterrupted early 1YR in 20 patients versus the seven patients who never reached 1YR: seizure frequency less than weekly versus weekly during the first year of treatment (P=0.0002) and idiopathic/cryptogenic versus symptomatic aetiology (P=0.0317). In contrast, pretreatment seizure frequency (P=0.1276), the epilepsy syndrome (P=0.1164), the type of epilepsy (P=0.1275), age of onset of epilepsy (P=0.1552) and gender (P=0.5969) were not significantly associated.

In multivariate analysis (Cox proportional hazards regression), seizure frequency less than weekly versus weekly during treatment (P=0.0125, hazard ratio 8.2 (1.6–43.0)) was significantly associated with entering uninterrupted early 1YR versus the seven who never reached 1YR. Idiopathic/cryptogenic versus symptomatic aetiology of epilepsy was not significantly associated with 1YR (P=0.6185).

One-year terminal remission
Seventy-eight (76%) of 102 patients had entered 1YTR (Fig. 1). Among the 78 patients entering 1YTR, 63 (81%) were free of AEDs at the end of follow-up. In univariate analysis (log rank test), three factors were associated with entering 1YTR: pretreatment seizure frequency of less than weekly versus weekly (P=0.0103), seizure frequency of less than weekly versus weekly during treatment (P=0.0001), and idiopathic/cryptogenic versus symptomatic aetiology (P=0.001). In contrast, main type of epilepsy (P=0.2948), epilepsy syndrome (P=0.1200), age of onset of epilepsy (P=0.9217) and gender (P=0.6222) were not significantly associated with entering 1YTR. Multivariate analysis (Cox proportional hazards regression) showed that seizure
Table 1 Clinical features of 102 patients including etiology, seizure frequency in the 12 months prior to and during the first year of drug treatment

<table>
<thead>
<tr>
<th></th>
<th>Idiopathic/symptomatic cryptogenic</th>
<th>Pretreatment seizure frequency</th>
<th>Treatment seizure frequency</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 66</td>
<td>n = 36</td>
<td>n = 65</td>
<td>n = 37</td>
</tr>
<tr>
<td></td>
<td>Mean (SD) Range</td>
<td>Mean (SD) Range</td>
<td>Mean (SD) Range</td>
<td>Mean (SD) Range</td>
</tr>
<tr>
<td>Age (surviving patients)</td>
<td>45.7 (4.5) 39–54</td>
<td>44.0 (4.9) 38–55</td>
<td>46.0 (4.6) 39–55</td>
<td>43.9 (4.3) 38–54</td>
</tr>
<tr>
<td>Age (dead)</td>
<td>30.0 (2.8) 28–32</td>
<td>26.1 (9.0) 11–38</td>
<td>27.5 (7.3) 13–38</td>
<td>24.7 (11.4) 11–36</td>
</tr>
<tr>
<td>Age at the onset</td>
<td>5.9 (4.3) 0–14</td>
<td>4.0 (4.4) 0–14</td>
<td>5.8 (4.5) 0–14</td>
<td>4.1 (4.1) 0–14</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Males</td>
<td>28 (42.4) 25 (69.4)</td>
<td>38 (58.5) 15 (40.5)</td>
<td>28 (43.8) 25 (65.8)</td>
<td>53 (52.0)</td>
</tr>
<tr>
<td>Females</td>
<td>38 (57.6) 11 (30.6)</td>
<td>27 (41.5) 22 (59.5)</td>
<td>36 (56.2) 13 (34.2)</td>
<td>49 (48.0)</td>
</tr>
<tr>
<td>Age at the onset</td>
<td>38 (57.6) 27 (75.0)</td>
<td>36 (55.4) 29 (78.4)</td>
<td>38 (59.4) 27 (71.0)</td>
<td>65 (63.7)</td>
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<tr>
<td>≤6 years</td>
<td>28 (42.4) 9 (25.0)</td>
<td>38 (44.6) 8 (21.6)</td>
<td>26 (40.6) 11 (29.0)</td>
<td>37 (36.3)</td>
</tr>
<tr>
<td>Type of epilepsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localization related</td>
<td>34 (51.5) 20 (35.6)</td>
<td>38 (58.5) 16 (43.2)</td>
<td>34 (53.1) 20 (52.6)</td>
<td>54 (52.9)</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>11 (16.7) 0 (0.0)</td>
<td>8 (12.3) 3 (8.1)</td>
<td>10 (15.6) 1 (2.6)</td>
<td>11 (10.8)</td>
</tr>
<tr>
<td>Rolandic</td>
<td>11 (16.7) 0 (0.0)</td>
<td>8 (12.3) 3 (8.1)</td>
<td>10 (15.6) 1 (2.6)</td>
<td>11 (10.8)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>16 (24.2) 20 (35.6)</td>
<td>25 (38.5) 11 (29.7)</td>
<td>18 (28.1) 18 (47.4)</td>
<td>36 (35.3)</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>11 (16.7) 13 (36.1)</td>
<td>17 (26.1) 7 (18.9)</td>
<td>11 (17.2) 13 (34.2)</td>
<td>24 (23.5)</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>1 (1.5) 2 (5.6)</td>
<td>1 (1.5) 2 (5.4)</td>
<td>1 (1.6) 2 (5.3)</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>2 (3.0) 0 (0.0)</td>
<td>1 (1.5) 1 (2.7)</td>
<td>2 (3.1) 0 (0.0)</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>Not localizable</td>
<td>2 (3.0) 5 (13.9)</td>
<td>6 (9.2) 1 (2.7)</td>
<td>4 (6.2) 3 (7.9)</td>
<td>7 (6.9)</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>7 (10.6) 0 (0.0)</td>
<td>5 (7.7) 2 (5.4)</td>
<td>6 (9.4) 1 (2.6)</td>
<td>7 (6.9)</td>
</tr>
<tr>
<td>Generalized</td>
<td>26 (39.4) 11 (30.6)</td>
<td>18 (48.6) 19 (36.3)</td>
<td>21 (32.8) 16 (42.1)</td>
<td>37 (36.3)</td>
</tr>
<tr>
<td>Childhood absence</td>
<td>25 (37.9) 0 (0.0)</td>
<td>15 (23.1) 10 (27.0)</td>
<td>19 (29.7) 6 (15.8)</td>
<td>25 (24.5)</td>
</tr>
<tr>
<td>Juvenile absence</td>
<td>5 (7.6) 0 (0.0)</td>
<td>2 (3.1) 3 (8.1)</td>
<td>3 (4.7) 2 (5.3)</td>
<td>5 (4.9)</td>
</tr>
<tr>
<td>Juvenile myoclonic</td>
<td>2 (3.0) 0 (0.0)</td>
<td>0 (0.0) 2 (5.4)</td>
<td>1 (1.6) 1 (2.6)</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>Awakening</td>
<td>1 (1.5) 0 (0.0)</td>
<td>1 (1.5) 0 (0.0)</td>
<td>1 (1.6) 0 (0.0)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Random generalized</td>
<td>6 (9.1) 0 (0.0)</td>
<td>5 (7.7) 1 (2.7)</td>
<td>6 (9.4) 0 (0.0)</td>
<td>6 (5.9)</td>
</tr>
<tr>
<td>Other primary</td>
<td>1 (1.5) 0 (0.0)</td>
<td>0 (0.0) 1 (2.7)</td>
<td>0 (0.0) 1 (2.6)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Generalized</td>
<td>1 (1.5) 11 (30.6)</td>
<td>3 (4.6) 9 (24.3)</td>
<td>2 (3.1) 10 (26.3)</td>
<td>12 (11.7)</td>
</tr>
<tr>
<td>West syndrome</td>
<td>0 (0.0) 8 (22.2)</td>
<td>3 (4.6) 5 (13.5)</td>
<td>3 (4.7) 5 (13.2)</td>
<td>8 (7.8)</td>
</tr>
<tr>
<td>Lennox-Gastaut syndrome</td>
<td>1 (1.5) 4 (11.1)</td>
<td>1 (1.5) 4 (10.8)</td>
<td>0 (0.0) 5 (13.2)</td>
<td>5 (4.9)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (9.1) 4 (11.1)</td>
<td>8 (12.3) 2 (5.4)</td>
<td>8 (12.5) 2 (5.3)</td>
<td>10 (9.8)</td>
</tr>
<tr>
<td>Undetermined whether focal or generalized</td>
<td>0 (0.0) 3 (8.3)</td>
<td>2 (3.1) 1 (2.7)</td>
<td>3 (4.7) 0 (0.0)</td>
<td>3 (8.3)</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td>6 (9.1) 2 (5.6)</td>
<td>7 (10.8) 1 (2.7)</td>
<td>6 (9.4) 2 (5.3)</td>
<td>8 (7.8)</td>
</tr>
</tbody>
</table>
frequency less than weekly versus weekly during treatment \(P = 0.0010\), hazard ratio 2.7 (1.5–5.0), pretreatment seizure frequency less than weekly versus weekly \(P = 0.0350\), hazard ratio 1.7 (1.04–2.9) were significantly associated with entering 1YTR. However, idiopathic/cryptogenic versus symptomatic aetiology \(P = 0.0627\) was not significantly associated with entering 1YTR. AUC was 0.77 for seizure frequency during treatment, 0.73 for aetiology of epilepsy and 0.64 for pretreatment seizure frequency. AUC was 0.84 when both significant factors, seizure frequency during treatment and pretreatment seizure frequency, were entered into the regression model.

Uninterrupted 1YTR

Figure 1 includes 20 patients with uninterrupted 1YTR who were seizure free on the first medication until the end of the follow-up. The follow-up of the 20 patients was 40 years (median 41.0, mean 39.1, SD 4.4, range 26–42). In univariate analysis (log rank test) only seizure frequency of less than weekly versus weekly during the first year of treatment \(P = 0.0048\) was associated with uninterrupted 1YTR. Pretreatment seizure frequency of less than weekly versus weekly \(P = 0.2640\) and idiopathic/cryptogenic versus symptomatic aetiology \(P = 0.2816\) were not significantly associated with uninterrupted 1YTR. In univariate Cox proportional hazards regression, seizure frequency less than weekly versus weekly during treatment the hazard ratio was 5.8 (1.3–25.1). In the next paragraph, we examine the impact of pretreatment seizure frequency on long-term seizure outcome.

Remission with regard to pretreatment seizure frequency

In the 65 patients having less than one pretreatment seizure per week group, the cumulative probability to be in 1YR was achieved in >90% during the first 10 years of follow-up (Fig. 2). Compared to the 37 patients with one or more seizures per week group, there was no significant difference in attaining a first 1YR \(P = 0.3825\). In the less than one pretreatment seizure per week group, the cumulative probability to be in 1YTR was achieved in more than 90% during the 40+ years of follow-up (Fig. 2). In contrast, among the 37 patients with one or more seizures per week group, only 69% achieved 1YTR during the 40+ years of follow-up \(P = 0.0103\), Fig. 2).

Twenty patients had uninterrupted 1YTR, with 15 in the less than one pretreatment seizure per week group and five patients in one or more seizures per week group \(P = 0.2640\), log rank). The cumulative probability to achieve an uninterrupted 1YTR during the observation period was 23% in the less than weekly pretreatment seizures group and 14% in the weekly seizures group \(P = 0.2640\), log rank). In the next paragraph, we compare the long-term seizure outcome in patients with less than weekly versus weekly seizure frequency during the first year of treatment.

Remission with regard to seizure frequency during the first year of treatment

We document first that treatment during the first year was adequate in terms of onset, dosage, choice of AEDs and drug compliance since the weekly seizure frequency after this treatment highly relies on that. There was no significant difference between the number of weeks from the onset of epilepsy to the start of treatment between patients with weekly versus less than weekly
seizure frequency during the first year of treatment. The start of treatment for those with weekly seizures was delayed for 8.0 weeks (median, 95% CI: 3.0–18.0) versus 2.0 (median, 95% CI: 1.0–8.0) for those with less than weekly seizures \((P = 0.0563)\). The longer delay in those with weekly seizures may be explained, at least in part, by the observation that many patients with weekly seizures had complex partial seizures that were not as easily and rapidly classified and treated as epileptic seizures. In contrast, those with less than weekly seizures often had generalized tonic–clonic seizures that were diagnosed and treated without delay. There was also no significant difference between the patients with weekly versus those with less than weekly seizures regarding the daily dosage of major AEDs. In more detail, the daily dosage of phenobarbital (phenemal) per kilogram body weight (mg/kg bw) was 3.8 (median, 95% CI: 3.0–4.5) for those with weekly seizures versus 3.2 (mg/kg bw) (95% CI: 2.9–3.7, \(P = 0.2502)\) for those with less than weekly seizures. For phenytoin it was 5.9 (mg/kg bw) (95% CI: 4.9–8.5) versus 6.7 (mg/kg bw) (95% CI: 5.0–7.7, \(P = 0.8824)\). For methylphenobarbital it was: 5.0 (mg/kg bw) (95% CI: 3.0–7.1) versus 4.8 (mg/kg bw) (95% CI: 2.7–9.1, \(P = 1.00)\). For primidone it was: 23 (mg/kg bw) (95% CI: 18.0–39.5) versus 18.5 (mg/kg bw) (95% CI: 7.9–49.0, \(P = 0.3458)\). Due to the small number of cases, the difference in dosage could not be calculated for ethosuximide (six cases); triethyloxazolidine (five cases); acetazolamide (three cases); carbamazepine (three cases) and methylisuximide (one case). We found no cases of worsening of generalized seizures that could be attributed to the choice of AEDs that work only for partial seizures.

The only significant difference between the weekly versus the less than weekly seizure groups was in the number of AEDs given during the first year of therapy. For the weekly seizure group the median was two AEDs (95% CI: 2.0–2.0) and in the less than weekly seizure group it was one (95% CI: 1.0–2.0, \(P = 0.0004)\), Mann– Whitney). Finally, we also determined AED intake adherence in both groups. We found no lack of adherence in those with weekly seizures. In fact, those with weekly seizures were even more compliant than those with less than weekly seizures. Fully regular ingestion of prescribed daily doses of AED(s) was documented in 72% of those with weekly seizures versus 64% in those with less than weekly seizures \((P = 0.8016)\).

In the less than one treatment seizure per week group, the cumulative probability was 95% to achieve 1YR ever within the first 10 years of follow-up (Fig. 3). In contrast, the 38 patients with one or more seizures per week group had significantly \((P = 0.0001)\) lower cumulative probability (76%) to attain 1YR ever in the same time period (Fig. 3). In the less than one treatment seizure per week group, the cumulative probability of 1YTR during the first 10 years of follow-up was 64% compared with 16% among 38 patients who had one or more seizures per week on treatment \((P = 0.0103)\) (Fig. 3).

Twenty patients had uninterrupted 1YTR, 18 in the less than one treatment seizure per week group and two patients with one or more seizures per week group \((P = 0.0048)\), log rank). The cumulative probability to achieve an uninterrupted 1YTR during the observation period was 28% in the less than weekly pretreatment seizures group and 5% in the weekly seizures group \((P = 0.0048)\), log rank). In the next paragraph, we compare the long-term seizure outcome in patients with different aetiology of their epilepsy.

**Remission with regard to aetiology of epilepsy**

In the 66 patients with idiopathic or cryptogenic aetiology, the cumulative probability to be in 1YR was more than 90% in the first 10 years of follow-up, but only 81% among the 36 patients with symptomatic aetiology to be in 1YR ever \((P = 0.0109)\) (Fig. 4). Although the cumulative probabilities being in first 1YR were lower in those with symptomatic aetiology, the probability increased with continued follow-up from 0.25 at 2 years to 0.90 at 40+ years (Fig. 4).

In 66 patients with idiopathic or cryptogenic aetiology, the first 10-year cumulative probability to enter 1YTR was 59% compared with 22% among the 36 patients with symptomatic aetiology \((P < 0.0001)\) (Fig. 4). Twenty patients had uninterrupted 1YTR, 15 of 66 (77%) with idiopathic/cryptogenic epilepsy group and five of 36 (86%) patients with symptomatic epilepsy \((P = 0.2816)\), log rank). In the previous sections, we assessed the isolated influence of either seizure frequency or aetiology on seizure outcome. In the next section, we determine the influence of the interaction of seizure frequency and aetiology on long-term seizure outcome.
Remission with regard to interaction of seizure frequency with aetiology of epilepsy

All patients with idiopathic or cryptogenic epilepsy having less than weekly pretreatment seizures entered 1YR during follow-up, as did 12 of 14 (86%) of patients with symptomatic epilepsy having weekly pretreatment seizures. It is reassuring that virtually all (51/52, 98%) children with low seizure frequency during the first year of treatment and idiopathic or cryptogenic aetiology will enter 1YR during the 40 years of follow-up, and almost all (49/52, 94%) will enter 1YTR. All the patients with symptomatic epilepsy having less than weekly seizures during the first year of treatment entered 1YR during follow-up, compared with only 19 of 24 (79%) of patients with symptomatic epilepsy having weekly treatment seizures.

When we analysed the interaction between pretreatment or treatment seizure frequency and idiopathic or cryptogenic versus symptomatic aetiology with the Cox model interaction, the $P$-values for 1YR and 1YTR were all non-significant ($P>0.05$). In the univariate Cox hazard regression, only the combination of idiopathic or cryptogenic aetiology and less than weekly treatment seizures was significantly associated with a higher 1YR ever [$P=0.0413$, hazard ratio 1.5 (1.02–2.3)].

Mortality outcome

Thirteen of 102 patients (13%) died during follow-up. The mean age at death was 24.7 (SD 11.4) years (median 26 years) for those with weekly pretreatment seizures and 27.5 (7.3) years (median 29 years) for those with less than weekly seizures ($P=0.9381$).

The duration of epilepsy before death was 22.5 (10.1) years, (median 23 years) for weekly seizures and 23.8 (7.4) years, [median 23 years ($P=0.8772$)] for less than weekly seizures. Cause of death was considered as epilepsy-related in six (46%), including sudden unexplained death in epilepsy (SUDEP), as defined above, in three, witnessed seizure in two and drowning in one patient. The remaining seven (54%) died from pneumonia ($n=2$), cardiovascular disorder ($n=4$) and massive haemorrhage associated with colitis ulcerosa ($n=1$).

As shown in Fig. 5, cumulative mortality was higher in patients with symptomatic versus idiopathic or cryptogenic aetiology having weekly pretreatment or treatment seizures (overall log rank $P<0.0001$, and $P<0.0001$). Pretreatment seizure frequency did not seem to influence mortality (overall log rank $P>0.6661$). Furthermore, mortality was not lower in those with symptomatic epilepsy having less than weekly seizures prior to or during treatment, except for a lower mortality after 40+ years of follow-up in the latter group.
compared to patients with either weekly seizures during treatment, cryptogenic/symptomatic aetiology or both ($P = 0.1069$). Thus, long-term mortality was not increased by having weekly seizures during the first year of treatment versus those with fewer seizures. In addition, pretreatment seizure frequency did not seem to determine mortality in idiopathic/cryptogenic versus symptomatic epilepsy (overall log rank $P = 0.6661$).

In univariate analysis (log rank test), mortality was significantly associated with aetiology (idiopathic/cryptogenic versus symptomatic, $P < 0.0001$) and seizure frequency during treatment ($P = 0.0105$). In multivariate analysis, however, the only significant predictor was aetiology [$P = 0.0071$, hazard ratio 9.0 (1.8–44.8)]. Pretreatment seizure frequency was not a significant predictor ($P = 0.3753$). AUC was 0.78 for aetiology of epilepsy, 0.68 for seizure frequency during treatment and 0.53 for pretreatment seizure frequency.

**Discussion**

The main findings of our study, to determine predictors of long-term seizure and mortality outcome in a population-based cohort of 102 patients followed-up for a median 40 years since their first seizure before the age of 16 years, are the following: (i) at the end of the very long follow-up, 95 (93%) of 102 patients had entered one or more 1YR. This included 20 patients with uninterrupted 1YR from the first year of treatment to the end of the follow-up and 78 patients with 1YR at the end of follow-up. In contrast, seven (7%) patients never experienced any 1YR and their epilepsy were considered drug-resistant, (ii) we found two predictors for adverse outcome which can be detected early in the course of treatment. Having weekly seizures during the first year of treatment carried an 8-fold risk [hazard ratio 8.2 (1.6–43.0), $P = 0.0125$] of developing drug resistant epilepsy and a 2-fold risk of never entering terminal 1YR [hazard ratio 2.7 (1.5–5.0), $P = 0.0010$]. Having weekly seizures prior to treatment only slightly increased the risk to never enter terminal 1YR [hazard ratio 1.7 (1.04–2.9), $P = 0.0350$]. (iii) Thirteen of 102 (13%) patients died during follow-up. Long-term mortality was 9-fold higher for patients with symptomatic epilepsy [hazard ratio 9.0 (1.8–44.8, $P = 0.0071$)], but was not increased by having weekly seizures prior to or during the first year of treatment versus fewer seizures. Our data indicate that seizure frequency in the first year of treatment allows predicting which children are becoming seizure-free for many years or destined to have drug-resistant epilepsy. Seizure frequency does not, however, seem to determine mortality. Symptomatic aetiology increases mortality and lowers the chance to enter 1YR and 1YTR. In addition, our finding that a low seizure frequency seems to predict better outcome only in those with idiopathic or cryptogenic aetiology (but not in those with symptomatic aetiology) is consistent with the hypothesis that symptomatic aetiology may over-ride seizure frequency as a determinant of drug-resistant epilepsy.

Long-term community-based studies of early predictors for medical intractability in childhood epilepsy are few in the recent literature (Sillanpää, 1993; Casetta et al., 1999; Spooner et al., 2006). Initial seizure frequency before therapy and remote symptomatic aetiology appeared to be a predictor for seizure control in a community-based case-control study of childhood-onset epilepsy with a median follow-up of 22 years (Casetta et al., 1999). An earlier study (Sillanpää, 1993) in a population which included both incident and prevalent cases, differed significantly from the present study which had a longer follow-up, and included only incident cases without a history of status epilepticus. Nevertheless, the earlier study with a follow-up of 30 years indicated that high initial seizure frequency and remote symptomatic aetiology were more common in drug resistant cases (Sillanpää, 1993). Since there is no agreed definition of drug-resistance, it is not surprising that a spectrum of criteria for drug resistance is found in the literature (Camfield and Camfield, 2003; Schmidt and Löscher, 2005). Our definition—never being seizure-free for 1 year during follow-up—is less restrictive than having annual seizures (Sillanpää, 1993; Loiseau and Jallon, 1995; Berg et al., 2001; Picot et al., 2008), monthly or weekly seizures despite treatment (Berg et al., 2001; Picot et al., 2008), but more restrictive than the definition of never entering five-year remission (Annegers et al., 1979; Sillanpää and Schmidt 2006; Sillanpää and Schmidt, 2008). If we apply the different criteria to our present study, 7% are considered drug-resistant by our criteria, 5% had on average one seizure per month and would be considered drug-resistant in other studies (Berg et al., 2001; Picot et al., 2008), including a surgery trial (Wiebe et al., 2001). Four per cent of our patients had, on average, four seizures every month, which is often used as an entry criterion for adjunctive drug trials in drug-resistant partial epilepsy (French et al., 2004). In a community-based cohort of 77 children with new-onset temporal lobe epilepsy, who were followed prospectively with formal review 7 and 14 years following seizure onset, only a lesion in the MRI indicating remote symptomatic aetiology, but not initial seizure frequency, and early seizure remissions were predictive of seizure outcome (Spooner et al., 2006).

Our data that symptomatic aetiology adversely affects seizure outcome are consistent with a MRI-based study with a shorter follow-up (Spooner et al., 2006). In the Connecticut study of childhood-onset epilepsy in 613 children with the mean follow-up of 4.8 years, a high initial seizure frequency and remote symptomatic aetiology negatively influenced the probability of remission (Berg et al., 2001). In addition, higher seizure frequency at presentation and/or remote symptomatic aetiology were also described as predictors of poor seizure outcome in several hospital- or practice-based studies of children or cohorts in children (Kwong et al., 2003; Gururaj et al., 2006; Wang et al., 2007) or that included children (Berg et al., 1996; Bertol et al., 1999; Ko and Holmes, 1999; Trinka et al., 2001). Response in the first 6–12 months on antiepileptic medication was shown to be predictive of outcome in a study of new-onset epilepsy in children seen in a single neurology practice (Oskoui et al., 2005). In the UK National General Practice Study of Epilepsy with a follow-up of 9 years that included childhood-onset cases, the only independent predictor of one-year and two-year remission was the number of seizures experienced by the patient in the 6 months after the first seizure (Cockerell et al., 1997; MacDonald et al., 2000).
As reviewed in the introduction, very few studies of death in epilepsy have included substantial number of children with a long-follow-up of 20 years or longer since the onset of their epilepsy (Sillanpää et al., 1995; Callenbach et al., 2001; Camfield et al., 2002). In our series, 13 of 102 (13%) patients died during follow-up. For reasons that may be related to a higher proportion of patients with symptomatic epilepsy, which was 36 of 102 (35%) in our series, our data showed a higher mortality rate than those reported in the literature. A Canadian population-based study reporting that 15% of children had a functional neurological deficit, showed 6.1% mortality 20 years after onset (Camfield et al., 2002). In the Connecticut study of epilepsy, with symptomatic aetiology in 20%, 13 of 613 children (2.1%) died seven months to 7 years after diagnosis (Berg et al., 2001, 2002). In a Dutch study (Callenbach et al., 2001), with 31% of children having symptomatic epilepsy, 1.9% of the children died during the study with a follow-up of 5 years or death. Although we had a similar rate of symptomatic epilepsy in our study, our mortality rate was higher, which may be related to the much longer follow-up in our study. Three of 102 children (3%) died from SUDEP which will be discussed in more detail in a separate publication. The study from Novia Scotia, which had a shorter follow-up, reported one case of probable SUDEP among 692 patients with childhood-onset epilepsy (Camfield et al., 2002). In our series, long-term mortality was 9-fold higher for patients with symptomatic epilepsy [hazard ratio 9.0 (1.8–44.8), P = 0.0071]. As in the literature, our data confirm that mortality increased with time (Kurtz et al., 1998), and most of the deaths were related to the presence of remote symptomatic aetiology or both and not directly to the seizures (Sillanpää et al., 1995; Callenbach et al., 2001; Camfield et al., 2002; Berg et al., 2004). The open question—if weekly seizure frequency in the first year of treatment determines increased mortality in childhood-onset epilepsy above the risk attributable to the underlying aetiology—has been answered. We found no evidence that having weekly seizures prior to or during the first year of treatment increased mortality. The result of multivariate analysis indicated that the only significant predictor was aetiology and may be explained as follows. Although both aetiology and seizure frequency, when examined separately, were significantly associated with mortality, they correlated with each other and subsequently contained overlapping information. When examined together, aetiology proved to cover the information included in the seizure frequency and thus aetiology alone can explain increased mortality. Our finding that a low seizure frequency during the first year of treatment does not seem to predict lower mortality, and that, conversely, a high seizure frequency does not predict increased mortality, is consistent with the hypothesis that symptomatic aetiology overrides inherent severity of the epilepsy, as indicated by the seizure frequency of the epilepsy, as a cause of mortality in epilepsy.

Although our population-based study has the advantage of a very long median follow-up (40 years) of children that developed epilepsy, this also contributes to its limitations. Limitations were that MRI data and modern treatment including newer antiepileptic drugs, resective surgery or vagus nerve stimulation were not available for most of the long-term study that began in the 1960s. The implications of our long-term study are 3-fold:

(i) Our study provides criteria to predict, after 1 year of treatment, which children are destined to develop drug resistant epilepsy. The treatment seizure frequency and remote symptomatic aetiology can be determined routinely. Evidence of first-year treatment seizures that occur once a week, or more often and symptomatic aetiology dramatically reduce the probability to become seizure free and to remain seizure free. Conversely, low seizure frequency seems to predict better outcome only in those with idiopathic or cryptogenic aetiology (but not in those with symptomatic aetiology). This suggests that symptomatic aetiology may override weekly seizure frequency as a determinant of drug-resistant epilepsy. Furthermore, symptomatic aetiology seems to increase the probability for mortality which is driven by the underlying causes of remote symptomatic epilepsy. The lack of MRI data in our series that started in the 1960s precludes further analysis of cause-specific mortality. Finally, it is interesting to note that weekly seizure frequency during the first year of treatment does not seem to predict increased mortality.

(ii) Our study does not provide absolute criteria for predicting drug-resistance. Despite having either a weekly seizure frequency or symptomatic epilepsy, 76–81% of children will have entered 1YR at 10 years of follow-up. In addition, the proportion of children entering 1YR in both groups will increase with further long-term follow-up. Despite having either a weekly seizure frequency or symptomatic epilepsy, 63–66% of children will have entered 1YTR at 40 years of follow-up. Even in the presence of a combination of frequent first-year treatment seizures and symptomatic aetiology, 19 of 24 (79%) of children will enter one or more periods of 1YR and one1YTR in nine of 24 (37%) in the course of their disorder. However, none of these 24 children can expect to remain seizure free from the start of treatment to the end of follow-up. It is reassuring that virtually all (51/52, 98%) children with low seizure frequency and non-symptomatic aetiology will enter 1YR during the 40 years of follow-up, and almost all (49/52, 94%) will enter 1YTR. In addition, as we have shown earlier, nearly one in five children whose epilepsy is initially well controlled later develop drug resistance (Sillanpää and Schmidt, 2006).

(iii) A combination of frequent pretreatment seizures and symptomatic aetiology will identify children destined to develop intractable epilepsy. This will allow evaluation of aggressive first-line treatment, perhaps even considering early invasive treatment after failure of a limited number of AEDs in children with a high risk for intractable epilepsy. Finally, better recognition and delineation of epilepsy through new diagnostic investigations may allow earlier and more effective treatment in the future that was not available when our study started 30–40 years ago.
Acknowledgements

We like to thank Olli Kaleva, BA (Turku, Finland) for computations.

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