A 15-year follow-up of first unprovoked seizures: a prospective study of 200 children

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ABSTRACT – Epilepsy is associated with an extended spectrum of behaviour, psychiatric problems, and learning difficulties. The aim of this study was to establish the natural history of children with first unprovoked seizures. We studied prospectively 200 children under the age of 11 years who attended hospital emergency with a first unprovoked seizure. Demographic variables, personal and family history, neurological examination, EEG, psychiatric, and cognitive and educational profiles were analysed. Patients who developed epilepsy were characterised with respect to: time to relapse, remission rate, duration of epilepsy, neuroimaging, aetiology, epileptic syndrome, and therapeutic regimen. These results were compared to data of patients who had a single seizure over a follow-up period of 15 years. Thirty percent of children who had a first unprovoked seizure developed epilepsy. Partial seizure type was a statistically significant variable for the development of epilepsy. An EEG with epileptic abnormalities proved to be the main risk factor for recurrence. Fifteen years later, the group with epilepsy exhibited a 2.6 greater risk of psychiatric and academic comorbidities, compared to the group without epilepsy.

Key words: children, epilepsy, comorbidities, first unprovoked seizure, follow-up

Epilepsy is defined as the tendency to have recurring unprovoked seizures (Berg and Scheffer, 2011) and is associated with an extended spectrum of behaviour, psychiatric problems, and learning difficulties. Prospective, population-based, studies demonstrate the existence of these comorbidities prior to the diagnosis of epilepsy and their persistence beyond the control of seizures (Berg et al., 2010). On the other hand, knowing the natural history of children with a first unprovoked seizure helps to establish criteria for the treatment and follow-up of epilepsy. Many cohort studies have addressed epidemiology, prognosis, and social and educational outcomes separately in children with epilepsy (Arts et al., 1999; Wakamoto et al., 2000; Hoie et al., 2005; Sillanpää and Schmidt, 2009; Geerts et al., 2010).
Other cohort studies have investigated the rate of recurrence and long-term outcome after first unprovoked seizures (Shinnar et al., 1996; Stroink et al., 1998; Berg et al., 2008), but few studies have compared the lifelong follow-up of children with single seizures who have or have not later developed epilepsy (Sogawa et al., 2010).

The purpose of this study was to establish the natural history of children with a first unprovoked seizure in order to compare between patients who later developed epilepsy with those who had a single seizure over a 15-year period, and thus identify significant prognostic factors for the development of epilepsy. In addition, we set out to compare the educational, psychiatric, and cognitive profile of the two patient groups.

Material and methods

Patients

We prospectively studied, over a 15-year period, 200 children who attended a tertiary referral hospital emergency centre, with a first unprovoked seizure, under the age of 11 years, between 1994 and 1997. Coimbra Pediatric Hospital, between 1994 and 1997, provided care only for children under the age of 13 years and its emergency centre served a population of 330,000 children. During this period, it was also the municipal hospital for children of Coimbra and a tertiary paediatric hospital for the central region of the country.

We divided the children in two groups: group 1 included patients who had at least two unprovoked seizures; and group 2 included children with a single seizure. Demographic variables, personal and family history, neurological examination, and EEG were analysed and compared between both groups. Psychiatric, cognitive, and educational profiles were assessed 2 and 15 years after the first seizure. We also characterised the group that developed epilepsy (group 1), considering: time to relapse, aetiology, epileptic syndrome, neuroimaging, therapeutic regimen, remission rate, and duration of epilepsy.

We carried out, after the first seizure, consultations at three, six and 12 months for all 200 children (groups 1 and 2). EEGs were scheduled before the first consultation in all cases. Neuroimaging studies (CT or MRI) were performed whenever clinically indicated. Cognitive assessment was performed in 69% of the cohort, between three and six months after the first seizure. Schedule of Growing Skills II was used for children of less than 6 years old (recently revalidated by Williams et al., 2013) and Wechsler Intelligence Scale-II for children of 6 years or older. Later, regular consultations were made for group 1, until the remission of epilepsy. Fifteen years later, a telephone interview was conducted for all children who had not been consulted regularly during follow-up. The response rate, based on the original 200 subjects, was 80%.

Definitions

A panel of two paediatric neurologists classified the seizures and epilepsies using the criteria and classification of the International League Against Epilepsy (Commission, 1989). Aetiology was considered as idiopathic, cryptogenic, or remote symptomatic (Commission, 1989). Recurrence was defined as an unprovoked seizure occurring more than 24 hours after the first seizure. Children were systematically not treated after the first seizure but could be treated after the recurrence. All EEGs were classified as normal or abnormal. We considered the presence of an abnormal background pattern (focal and generalised slowing) or the presence of epileptiform abnormalities (focal and generalised spikes or spike-wave complexes) to be abnormal. Mild intellectual disability was defined for children with IQ in the range 50 to 69; moderate intellectual disability for IQ in the range 35 to 49, and severe intellectual disability for IQ in the range 20 to 34 (ICD-10). We defined “academic difficulties” as difficulties that interfere in reading, writing, and mathematics in children with normal IQ (DSM IV).

For group 1, the timing of relapse was considered; the period between the first and second seizure. Medically intractable epilepsy was defined as epilepsy that was not controlled by two or more antiepileptic drugs (AEDs) used in the optimal dosage and the patient continued to have seizures even after two years of treatment (Commission, 1989). The term “remission” is used here to describe a continuous five-year period of seizure freedom (Commission, 1989).

Exclusion criteria

Children with neonatal seizures, myoclonic seizures, absences, infantile spasms, and epileptic encephalopathy were excluded.

Statistical analysis

Statistical analysis was performed using SPSS 20. Categorical data are shown as proportions and continuous variables as mean +/- SD or Median (IQR) as adequate. Comparison between groups was analysed through Independent Samples T Test, considering normal distribution based on Central Limit Theorem (n>30). For categorical variables, comparison between groups was performed using $\chi^2$ or Exact Fisher as adequate. Variables with $p<0.10$ in univariate analysis were included in the logistic regression, enter mode. $P$ values $<0.05$ were considered as significant in all statistical analysis.
Written informed consent was given by all parents. The hospital ethics committee approved the study.

Results
A total of 200 children with a first unprovoked seizure were analysed; 53% were male. At two years follow-up, there were 56 children in group 1 and 144 in group 2. During the period of the study, 30% ($n=61$) developed epilepsy.

Age and clinical presentation
The median age at first seizure was 6 years in group 1 (mean: 5.4; range: 4 months to 10 years) and 4 years in group 2 (mean: 4.2; range: 5 months to 10 years). In this study, the youngest age at first unprovoked seizure was a statistically significant factor for no recurrence ($p=0.007$).

In group 1, 26 of 56 (47%) children presented with a partial seizure and 24 of 56 (43%) presented with a generalised seizure (for the remaining 10%, the type of seizure could not be accurately defined). Group 2 had more generalised seizures at presentation; 96 of 144 (66%) had generalised seizures and 24 of 144 (17%) had partial seizures (for 17%, the seizures were undefined). In this study, partial seizure type was a statistically significant variable for the development of epilepsy ($p=0.000$).

EEG at presentation
Group 1 had abnormal EEG in 41 of 56 cases (73%). In this group, abnormalities were focal in 48%, generalised in 18%, and EEG showed background slow activity in 7% of cases. Group 2 had abnormal EEG in 55 of 144 cases (38%), with generalised anomalies in 28%, focal anomalies in 3%, and background slow activity in 7%. Statistical analysis showed that an abnormal EEG proved to be the main risk factor for recurrence ($p=0.000$).

Cognitive assessment
The cognitive assessment was performed in 69% of the cohort. The mean IQ in group 1, performed in 44 children, was 94 (range: 30-121). The mean IQ in group 2, performed in 95 children, was 100 (range: 54-130). Despite the mean IQ being slightly higher in the group without epilepsy, there was no statistically significant difference between the two groups with regards to cognition.

Other variables
There was no significant difference between the two groups with respect to: history of febrile seizures, complications in the neonatal period, family history of epilepsy, or neurological examination.

Timing of relapse
Twenty-nine children (48%) relapsed within the first three months and 93% during the first year. Only 7% ($n=5$) relapsed after the first year (figure 1). Curiously, we did not observe recurrence during the second year of follow-up. The median time to relapse was five months (range: 3 months to 5 years).

Epilepsy classification, syndromes and aetiology
Regarding only group 1, localisation-related epilepsy was the most frequent type of epilepsy ($n=40$; 65%) and within this, benign childhood epilepsy with centro-temporal spikes (BECTS) was the main epileptic syndrome recognised (30%). Generalised epilepsy corresponded to 25% ($n=15$) of cases. Specific syndromes and undetermined aetiology accounted for 10% ($n=6$). Aetiology was considered idiopathic in 54% ($n=33$) of the cohort (group 1), cryptogenic in 18% ($n=11$), and symptomatic in 28% ($n=17$).

Neuroimaging
Neuroimaging (CT or MRI) was performed in 70% of children with epilepsy (group 1) and was abnormal in 25%. However, the changes were directly related to epilepsy in only in two cases (one case with sequelae lesions of hypoxic-ischaemic encephalopathy and another case with left opercular atrophy). The remaining 30%, who did not undergo neuroimaging, corresponded to children with BECTS. Children with a single seizure do not routinely undergo neuroimaging.

Treatment
No antiepileptic drugs were prescribed after the first seizure.
At two years follow-up, 45 children with a defined epilepsy (belonging to group 1) had been treated with AEDs (72%) and 11 (18%) were not treated. Forty-five percent received valproic acid and 33% carbamazepine. Only 2 children (4%) required polytherapy. Fifteen years later, only 12 children from group 1 were still taking AEDs.

Figure 1. Timing of relapse in the epilepsy group.
Risk of recurrence
Based on univariate analysis, we found that there was a greater risk of recurrence with older age at first seizure, when the first seizure was partial and when EEG presented epileptic abnormalities. These variables were also included in the logistic regression analysis.

Based on a multivariate logistic regression analysis, the type of seizure (B: -3.104; \(X^2\) Wald 16.708, \(p<0.001\), OR: 0.45) and abnormal EEG (B: 3.364, \(X^2\) Wald: 18.48, \(p<0.001\), OR: 28.908) remained independent predictors of seizure recurrence, while the predictive value of age at first seizure was lost.

Course of epilepsy
After the 15-year follow-up period, the response rate based on the original 200 subjects was 80% (\(n=159\)). Of these, 52 corresponded to group 1 and 107 to group 2. Two children died and 39 (from group 2) did not participate in the telephone interview. The mean interval between the very first seizure and the last reported seizure, during this study, was 5 years (range: 9 months to 15 years). Currently, 77% of patients are seizure-free and off therapy. Epilepsy remains active in 12 children (20%) and intractable in 6 (11.5%). Remission rate at 5 years was 59% and at 15 years was 80% (figure 2).

Comorbidities
After the 15-year follow-up period, a significant number of psychiatric and academic comorbidities were identified. The group with epilepsy had a 2.6 greater risk of global comorbidities than the group without epilepsy (\(p=0.011\)). In particular, learning disabilities were present in 15 of 52 children (30%) in group 1 and 4 of 107 children (4%) in group 2. Attention deficit with hyperactivity disorder (ADHD) affected 7 of 52 cases (13%) in group 1 and 5 of 107 cases (5%) in group 2. Intellectual disability was present in 9% (5 cases) in group 1 and 2% (2 cases) in group 2 (table 1).

Patients in group 1 required more school support, by a factor of 1.8, compared to those in group 2 (\(p=0.036\)). Thirty-three percent (17 of 52) in group 1 received school support in comparison to 18% (19 of 107) in group 2 (table 1). Nine children (18%) required a specialised school in group 1 versus only 2 children (2%) in group 2.

Antiepileptic or psychiatric drugs were used more frequently in group 1, by a factor of 4.7 (\(p=0.000\)). Ten of 52 children (20%) and 11 of 107 patients (10%) were treated with psychiatric drugs in group 1 and 2, respectively. We considered methylphenidate to be a psychiatric drug, which was used by 8 children (table 1).

Mortality
Two of the 200 children died during the follow-up period. The causes of death were not related to the epilepsy. The mortality rate in our study was 0.67‰ per year.

Discussion
The aim of this prospective study of 200 children was to establish the natural history of children with first unprovoked seizures, further characterise those that developed epilepsy, and compare these results with patients who had a single seizure.

Prior studies have shown that recurrence after a single unprovoked seizure in childhood is about 50% (Berg and Shinnar, 1991; Shinnar et al., 1996; Stroink et al., 1998; Shinnar et al., 2000; Eden et al., 2006; Arts and Geerts, 2009). In our study, 30% of children who had a first unprovoked seizure developed epilepsy. The Dutch Study (Stroink et al., 1998), that included a cohort of 156 children presenting with a single seizure, aged 1 month to 16 years, found that the overall recurrence rate after two years was 54%. In the FIRST Study (Musicco et al., 1997) and MESS Study (Kim et al., 2006), the overall recurrence rate after two years was 51% and 39%, respectively. However, these last two studies did not include only paediatric patients. Perhaps our lower rate of recurrence is due to our greater percentage of idiopathic cases and to our exclusion criteria. Neonatal seizures, myoclonic seizures, absences, infantile spasms, and epileptic encephalopathy were all excluded, leaving us with epilepsies that are not so severe.

The risk factors for recurrence, identified in this study, were similar to those reported by others (Berg and Shinnar, 1991; Shinnar et al., 1996; Stroink et al., 1998). An EEG with epileptic abnormalities proved to be the main risk factor for recurrence. Another factor associated with a higher risk of recurrence was seizure type; i.e. partial seizures. Other factors identified by previous studies (Shinnar et al., 1996; Stroink et al.,...
Table 1. Comparison of comorbidities, educational profile, and treatment in children with epilepsy (group 1) and a single seizure (group 2).

<table>
<thead>
<tr>
<th></th>
<th>Group 1 n=52 (%)</th>
<th>Group 2 n=107 (%)</th>
<th>Relative risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Learning difficulties</td>
<td>15 (30)</td>
<td>4 (4)</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>Psychiatric</td>
<td>10 (19)</td>
<td>18 (17)</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>ADHD</td>
<td>7 (13)</td>
<td>5 (5)</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Intellectual disability</td>
<td>5 (9)</td>
<td>2 (2)</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td><strong>Educational profile</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular class</td>
<td>35 (67)</td>
<td>88 (82)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>With support</td>
<td>17 (33)</td>
<td>19 (18)</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Special class</td>
<td>9 (18)</td>
<td>2 (2)</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AED</td>
<td>10 (19)</td>
<td>0 (0)</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>Psychiatric drugs</td>
<td>8 (16)</td>
<td>11 (10)</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>AED+psychiatric drugs</td>
<td>2 (4)</td>
<td>0 (0)</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

ADHD: attention deficit with hyperactivity disorder; AED: antiepileptic drug.
*AED therapy was only started after two or more seizures.

1998), such as history of febrile seizures, complications in the neonatal period, family history of epilepsy, and abnormalities based on neurological examination had no influence on our recurrence rate.

Regarding the time of relapse, 48% (n=29) relapsed in the first 3 months and 93% relapsed in the first 12 months. In our study, the probability of developing epilepsy after a first unprovoked seizure was very low after the first year (figure 1). The median time to recurrence was 5 months (range: 3 months to 5 years) which is consistent with data from other studies (Shinnar et al., 1996; Stroink et al., 1998).

Regarding the group that developed epilepsy, BECTS was recognised as the main epileptic syndrome (30%). Wakamoto et al. followed 155 individuals with childhood-onset epilepsy, and also found that the most common epileptic syndrome was BECTS (21.5%). The slightly higher percentage of BECTS in the present study may be attributed to slight differences in the age of this cohort, which was lower in our study (0-11 years) and due to the nature of recruitment of our children, who were approached via the hospital emergency department. The manifestation of a single seizure is not a feature of many other types of epilepsy. In this study, the mean duration of epilepsy was 5 years, overlapping the Dutch Study (Stroink et al., 1998), in which the mean duration of epilepsy was 6 years.

The final outcome demonstrates that the majority of children with epilepsy had a good outcome, with 70% in remission for at least 5 years. This finding is comparable with the Dutch Study (a prospective hospital-based study) of 413 children (Geerts et al., 2010), the Finnish Study (a population-based study) of 144 children (Sillanpää and Schmidt, 2009), and a retrospective hospital-based study of 148 children with epilepsy (Wakamoto et al., 2000). For these studies, with a follow-up of 15, 37, and 19 years, the proportion of patients in 5-year terminal remission was 71%, 67%, and 63%, respectively.

Epilepsy remained active in 12 children (20%) and intractable in 6 (11.5%). This data is also in agreement with the Dutch Study (Geerts et al., 2010) in which, after a 15-year follow-up period, epilepsy remained active in 29% and intractable in 8.5%.

In addition, we set out to compare psychiatric, cognitive, and educational profiles of both groups, at the end of the follow-up period. After 15 years, we observed a large number of psychiatric and academic comorbidities; the group with epilepsy had a 2.6 greater risk of comorbidities (p=0.011). Learning difficulties, ADHD, and intellectual disability were the most important comorbidities identified. Once more, we could conclude that group 1 with epilepsy required much more school support than group 2 (33% vs. 18%; table 1), even considering that 71% of the epilepsy group had normal IQ.

A recent study in the United States (Sogawa et al., 2010) showed that 40% of children with epilepsy versus 28% of children with a single seizure received special education or repeated a grade. In our study, 67% of children with epilepsy attended regular classes in standard schools, in agreement with the Wakamoto survey in Japan that found similar results (71.6%). In our group with epilepsy, 18% required special education and this
is consistent with the Dutch Study in which 18/151 subjects (12%) underwent special education (Geerts et al., 2011).

Antiepileptic and psychotropic drugs, especially methylphenidate, were used 4.7 times more frequently in the epilepsy group ($p=0.000$).

The mortality rate in our study was 0.67‰ per year. This is the lowest mortality rate finding in a first unprovoked seizure or epilepsy studies in childhood (Sillanpää and Schmidt [2009] reported 1.3‰ per year and Geerts et al. [2010] reported 2.7‰ per year). This rate is probably caused by the selection criteria of the cohort (presentation with just one unprovoked seizure).

In this prospective cohort study, there are, however, two main limitations: regular visits were made over only a year for the group that did not relapse, and the comorbidities in this group were identified by telephone interview which may have led to an underestimate. However, after 15 years, we observed a large percentage of psychiatric and educational comorbidities in a population with benign epilepsy and the persistence of these comorbidities well after the control/cure of epilepsy.

**Disclosures.**

None of the authors have any conflict of interest or financial support to disclose.

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