

The first unprovoked, untreated seizure in childhood: a hospital based study of the accuracy of the diagnosis, rate of recurrence, and long term outcome after recurrence. Dutch study of epilepsy in childhood

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Abstract

Objective—To assess the accuracy of the diagnosis of a first unprovoked seizure in childhood, the recurrence rate within two years, the risk factors for recurrence, and the long term outcome two years after recurrence.

Methods—One hundred and fifty six children aged 1 month to 16 years after a first seizure, and 51 children with a single disputable event were followed up. The diagnosis of a seizure was confirmed by a panel of three child neurologists on the basis of predescribed diagnostic criteria. None of the children was treated after the first episode.

Results—Five children with a disputable event developed epileptic seizures during follow up. The diagnosis did not have to be revised in any of the 156 children with a first seizure. The overall recurrence rate after two years was 54%. Significant risk factors were an epileptiform EEG (recurrence rate 71%) and remote symptomatic aetiology and/or mental retardation (recurrence rate 74%). For the 85 children with one or more recurrences, terminal remission irrespective of treatment two years after the first recurrence was >12 months in 50 (59%), <six months in 22 (26%), and six to 12 months in 11 (13%) and unknown in two (2%). Taking the no recurrence and recurrence groups together, a terminal remission of at least 12 months was present in 121 out of the 156 children (78%).

Conclusions—The diagnosis of a first seizure can be made accurately with the help of strict diagnostic criteria. The use of these criteria may have contributed to the rather high risk of recurrence in this series. However, the overall prognosis for a child presenting with a single seizure is excellent, even if treatment with antiepileptic drugs is not immediately instituted.

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Despite several studies,¹⁻¹² there is still no definite answer concerning the management strategy of children with a first unprovoked epileptic seizure. Besides knowledge of the risk of

recurrence and the predictive factors, knowledge of the long term prognosis after a recurrence is a prerequisite for the formulation of adequate treatment guidelines.

Reported estimates of the recurrence risk after a first unprovoked seizure in childhood range from 23% to 71% after three years.²⁻⁴ The main factors associated with a higher risk of recurrence are an EEG showing epileptiform abnormalities and remote symptomatic aetiology.¹²

Possible causes for the widely diverging recurrence rates are differences of study design, case definitions used for ascertainment, referral patterns within the population studied, delay after the seizure before inclusion in the study, and the prevalence of various potential risk factors within the population studied.¹²⁻¹³ A surprising factor is the absence of discussion about diagnostic uncertainty. In none of the studies mentioned above have diagnostic criteria been used to differentiate between epileptic and non-epileptic first fits. In particular in young children and infants the differential diagnosis of a seizure is extensive, and confirming or refuting the epileptic origin of such an event may be quite difficult.

It is still a matter of discussion whether or not children should be treated after a first unprovoked seizure. Treatment after a first fit may lead to a significant decrease in the risk of relapse.¹¹ Whether early suppression of seizures contributes to a better long term outcome after recurrence, however, has not yet been defined.

This study was designed to assess prospectively the risk of recurrence in an accurately diagnosed cohort of children with an untreated first unprovoked seizure, to identify predictive factors for such a recurrence, and to estimate the long term outcome of those children who had a relapse. To improve diagnostic accuracy, we used predefined diagnostic criteria formulated in simple descriptive terms, as well as the expert opinion of a panel of paediatric neurologists.

Methods

PATIENTS

Most patients in this prospective study were derived from a consecutive series of 850 children, aged between 1 month and 16 years, who were referred with one or more possible unprovoked seizures, or at least one episode of

Table 1 Association between originally defined risk factors and risk of recurrence after a first seizure: univariate analysis with Cox's proportional hazards regression model

Risk factors	Rate ratio	95% CI	p Value
Age at intake (n=156)	1.02	0.97-1.08	0.43
Patient delay (n=156)	0.99	0.97-1.00	0.06
Sex:			
Male (n=70)	1.00†		
Female (n=86)	0.73	0.48-1.12	0.15
Seizure type (description only):			
Tonic clonic (n=142)	1.00†		0.95
Complex partial (n=8)	0.99	0.36-2.72	0.99
Simple partial (n=6)	1.18	0.43-3.23	0.75
Seizure type (description and EEG combined):			
Generalised (n=84)	1.00†		0.19
Partial (n=63)	1.50	0.97-2.33	0.07
Undefined (n=9)	1.35	0.53-3.41	0.53
Aetiology:			
Idiopathic/cryptogenic (n=129)	1.00†		
Remote symptomatic (n=27)	2.25	1.37-3.70	0.001*
EEG1:			
Normal (n=57)	1.00†		
Epileptiform (n=68)	2.45	1.49-4.03	0.0004*
Other abnormalities (n=31)	1.02	0.52-2.02	0.94
EEG2:			
Normal (n=39)	1.00†		
Epileptiform (n=20)	1.05	0.44-2.51	0.91
Other abnormalities (n=13)	2.70	1.16-6.28	0.02*
EEG1 and EEG2 combined:			
Normal (n=43)	1.00†		
Epileptiform (n=88)	2.04	1.18-3.52	0.01*
Other abnormalities (n=25)	1.18	0.55-2.53	0.66
CT-brain:			
Normal (n=100)	1.00†		
Abnormal (n=12)	1.96	1.00-3.87	0.05*
Not done (n=44)	0.69	0.41-1.17	0.17
Family history for epilepsy:			
Negative (n=141)	1.00†		
Positive (n=15)	0.77	0.35-1.66	0.50
History of febrile convulsions:			
Negative (n=139)	1.00†		
Positive (n=17)	0.82	0.40-1.70	0.59
State of arousal:			
Awake (n=100)	1.00†		
Sleep (=42)	0.73	0.44-1.22	0.23
On awakening (n=9)	1.04	0.42-2.59	0.94
Unknown (n=5)	1.87	0.67-5.17	0.23

*Statistically significant. †Reference category.

status epilepticus, to one of the four participating hospitals: two university hospitals, one children's hospital, and one general hospital in the southwest region of The Netherlands. This cohort forms the basis of the Dutch Study of Epilepsy in Childhood (DSEC), which tries to answer several clinical-epidemiological questions about newly diagnosed childhood epilepsy.¹⁴ Inclusion for the first seizure part of

the DSEC started 1 January 1988 and ended 1 August 1992. Children were mainly referred by general practitioners, by paediatricians of the participating hospitals, or were first seen in the emergency room of the participating hospitals. All children with possible seizures were recruited, but to be eligible for entry into the study, a committee of paediatric neurologists (HS, WFA, OFB, and ACBP, excluding the attending neurologist) had to agree that the description of the single episode, as described by the child, or an eye witness, or both concurred with predefined descriptive diagnostic criteria of an epileptic seizure, adapted from Van Donselaar *et al* (1989),¹⁵ without having any knowledge of the results of the EEG. The committee excluded children with a clear non-epileptic event such as a reflex anoxic seizure or syncope. Children with an event classified by the committee as "disputable" were followed up separately for one year to test our diagnostic procedure.

Children with a seizure due to an acute neurological insult (meningitis, trauma), metabolic disturbances, or fever (temperature over 38.0°C) were excluded. Children with a history of earlier seizures other than neonatal or febrile seizures; with a single episode of status epilepticus; with a recurrence within 24 hours; or with an interval between the seizure and the first visit to the hospital of more than three months, were not included in the first seizure part of the DSEC, but in the study part on the general prognosis of newly diagnosed epilepsy in childhood (Arts *et al*, unpublished data). Of the remaining 171, we excluded 11 children because of possible fever reported by the parents (precise temperature not known). Four other children were excluded because they had been treated with antiepileptic drugs. One child was treated mistakenly after only one seizure; three other children were treated because of multiple recurrences associated with fever, but they had not had unprovoked recurrences at that time. Finally 156 children remained for inclusion.

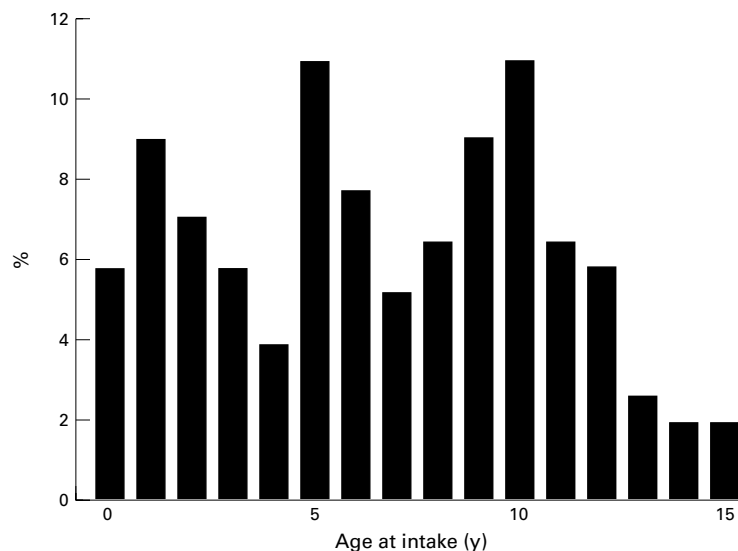


Figure 1 Distribution of ages of 156 children at the time of their first unprovoked seizure.

CLASSIFICATION

The committee classified seizures according to the revised classification of the International League Against Epilepsy (ILAE).¹⁶ The aetiology was classified as remote symptomatic if the child was known to have a static encephalopathy caused by a prenatal or perinatal encephalopathy or a prior neurological insult such as infection, stroke, or cerebral trauma. Children with mental retardation (estimated IQ below 70) were included in this group. According to the recent guidelines on epidemiological research of the ILAE,¹⁷ patients with a genetically determined type of epilepsy manifesting through a single seizure were called idiopathic. All other children were considered cryptogenic. In this analysis idiopathic and cryptogenic cases were grouped together. This seems to be justifiable, because it is usually not possible to distinguish between them after only one seizure.¹⁸

Table 2 Outcome of 51 children with a disputable episode

Probable diagnosis after 1 year	n	Epileptiform discharges on EEG1	Children with recurrences
Epilepsy	5	3	5
Found in supposedly postictal state	4	1	0
Seizure not meeting the criteria	3	1	0
Syncope	13	1	2
Breath holding spells	2	0	1
Benign paroxysmal vertigo	1	0	1
Pseudoseizures	1	0	1
Pavor nocturnus	1	0	1
No diagnosis	20	2	2
Lost	1	0	?
Total	51	8	13

ADDITIONAL INVESTIGATIONS

A standard EEG (EEG1) was obtained in all patients. If it did not disclose epileptiform abnormalities, a second EEG (EEG2) was performed after partial sleep deprivation, or during the daytime sleep in very young children. All EEGs were classified as normal or abnormal and scored for the presence of epileptiform abnormalities (focal and generalised spikes or spike and wave complexes), and other abnormalities (abnormal background pattern or focal non-epileptiform abnormalities) by clinical neurophysiologists who were unaware of the clinical data.

Brain CT was scheduled in all children if possible without anaesthesia. The decision to perform CT in the remaining children was up to the child neurologist.

FOLLOW UP

We followed up all children with a single seizure on a regular basis for 24 months by hospital visits and by telephone interviews. After a recurrence, defined as any unprovoked seizure after inclusion into the study, the children were seen again and a detailed history was taken. We followed up all these children after their recurrence for 24–72 months (mean 42, median 44, 25, and 75 percentile: 30; 54 months) until 1 August 1994, with the exception of two children who were lost 0 and 10 months after the recurrence.

No antiepileptic drugs were prescribed after the first seizure. The decision whether or not to start treatment after one or more recurrences was left to the attending paediatric neurologist.

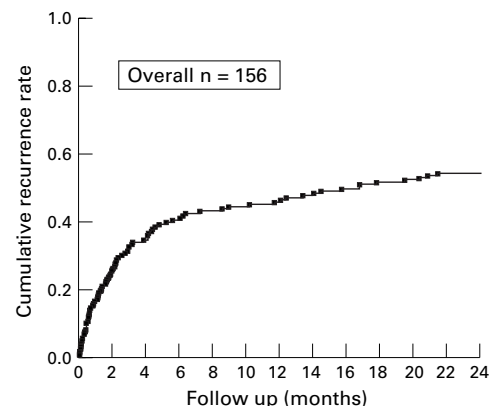


Figure 2 Probability of recurrence of seizure after a first unprovoked seizure.

The outcome was measured by two methods. Firstly, the duration of the seizure free period irrespective of treatment existing at two years after the first recurrence (terminal remission, TR) according to the following definition: excellent, no recurrence at all; good, TR at least 12 months; moderate, TR six to 12 months; poor, TR less than six months. Secondly, the maximum period of seizure freedom after recurrence irrespective of treatment (longest remission ever, LRE) according to a slight modification of the definition of Arts *et al*¹⁹: excellent, no seizures at all; good, LRE at least 12 months; moderate, LRE 6 to 12 months; poor, LRE less than 6 months.

Fifty one children with a single ictal event in whom no clear diagnosis could be made were followed up for one year to assess the accuracy of our diagnostic procedure.

ANALYSIS

Kaplan-Meier survival analysis was used for calculation of the recurrence rates.²⁰ Univariate and multivariate analyses were performed using Cox's proportional hazards model.²¹ The multivariate analysis was done with a full model and with stepwise backward elimination of variables. In the second, we used simple parameter coding, and a probability of removal of 0.10.

INFORMED CONSENT

The study was approved by the ethics committees of all involved hospitals, and informed consent was obtained in all cases before enrolment.

Results

Seventy of the 156 included children were boys (table 1); the mean age at intake was 7.1 years (median 6.9; range 0.2–15.6 years) (fig 1); 49% of the children were seen within 24 hours after the seizure; 71% within one week; 89% within one month; and all were seen within 81 days.

According to the predefined descriptive criteria, 142 children had a generalised tonic-clonic seizure with or without partial onset, eight a complex partial seizure, and six a simple partial seizure without secondary generalisation. The standard EEG showed abnormalities in 99 (63%).

DIAGNOSTIC ACCURACY

We excluded 51 children with a single episode, judged by the committee as being of disputable origin (table 2). One child was lost to follow up. Five children (10%) proved to have epilepsy during a one year follow up. Three of these had epileptiform discharges in their standard EEG. Four children with a disputable event had been found unconscious in a possible postictal state, without a seizure itself having been witnessed. Three other children had had a seizure according to the committee, but the description did not meet the a priori descriptive criteria. These seven children did not have a recurrence within one year, although two had epileptiform discharges on EEG1. The other children turned out to have vasovagal syncope (13), blue or pale breath holding spells (two), benign

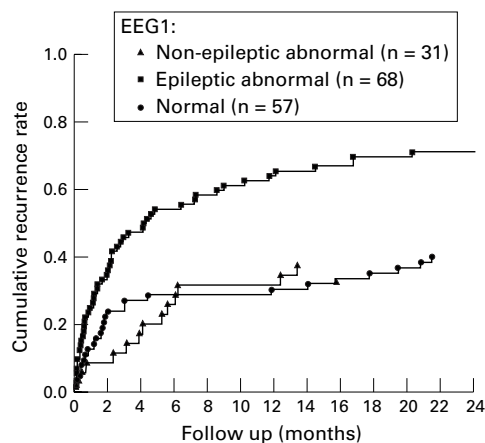


Figure 3 Probability of recurrence of seizure after a first unprovoked seizure as function of the standard EEG.

paroxysmal vertigo (one), pseudoseizures (one), pavor nocturnus (one), or the nature of the episodes remained unresolved during follow up (20). Yet, three of them had epileptic discharges on the EEG. This was interpreted as a coincidence.

The diagnostic accuracy in the 156 children in whom the panel confirmed the diagnosis of a seizure was high. The diagnosis was not revised in any of the children with a recurrence of the event.

RISK OF RECURRENCE

The overall recurrence rate was 40% (95% confidence interval (95% CI) 33–48%) at six months; 46% (95% CI 38–53%) at one year; and 54% (95% CI 46–62%) at two years (fig 2). Significant predictive factors for recurrence were results of EEG1 and EEG2, aetiology, and CT (table 1).

Children with epileptic discharges in their EEG1 (n=68; 44%) had a recurrence rate of 71% at two years (95% CI 60–81%); in children with a normal EEG1 (57) this was 40% (95% CI 28–53%), and in those (31) with an otherwise abnormal EEG1 42% (95% CI 25–59%) (fig 3). A second EEG, performed in 72 of 88 children who had no epileptic discharges on EEG1, showed epileptiform abnormalities in another 20 children (28%).

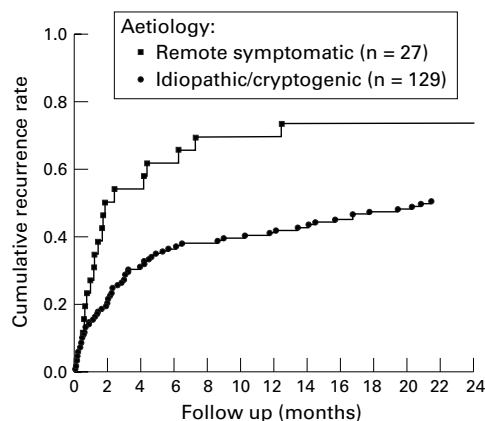


Figure 4 Probability of recurrence of seizure after a first unprovoked idiopathic or cryptogenic seizure and after a first unprovoked remote symptomatic seizure.

Aetiology also proved to be a significant predictive factor for recurrence (fig 4). Recurrence rate at two years was 50% (95% CI 41–59%) in 129 children with a cryptogenic or idiopathic seizure, and 74% (95% CI 57–91%) in 27 children with remote symptomatic aetiology or mental retardation without known cause (table 1).

Brain CT was obtained in 112 children. The abnormalities (mostly atrophy) found in 12 children were without therapeutic consequences. Recurrence rate at two years was 75% (95% CI 51–100%) in those with abnormal CT findings, 56% (95% CI 46–66%) in the children with normal CT and 43% (95% CI: 29–58%) in the children in whom no CT was performed.

No significant influence on the recurrence rate was found for the other variables investigated (table 1).

Full model multivariate analysis was carried out with 11 variables. An epileptiform EEG1 was the most important predictive factor for seizure recurrence. Remote symptomatic aetiology was also significantly associated with risk of recurrence. After stepwise backward elimination of variables not contributing to the model, aetiology, EEG1, and the sleep state remained. EEG1 was the most significant variable.

LONG TERM OUTCOME AFTER RECURRENCE

At the end of the follow up of all children, 71 children (46%) had an excellent outcome without any recurrent seizure. Sixty nine Of the 85 children with a recurrence were treated with antiepileptic drugs. Of the children with a recurrence, 27 (32%) had an excellent outcome, 23 (27%) a good, 11 (13%) a moderate, and 22 (26%) a poor outcome defined by terminal remission. Two children were lost 0 and 10 months after recurrence. This means that of all admitted children with a single seizure 121 (78%) had an excellent or good outcome. According to the definition of Arts *et al*⁹ the outcome was excellent in 27 children (32%) with a recurrence, good in 32 (38%) moderate in 17 (20%) and poor in only seven (8%). The outcome was excellent or good in 130 (83%) of all admitted children.

Discussion

When the clinician is confronted with the problem of a child who has experienced a single episode that seems to be of epileptic origin, some questions have to be considered. Was the event really epileptic? If so, what is the risk of more seizures occurring? Should anticonvulsant treatment be offered and with what goal? What is the long term outcome with or without treatment?

As the diagnosis of a first epileptic seizure may have a great impact on the child and its parents, a correct diagnosis is of the utmost importance. Criteria for the diagnosis single seizure are not discussed in earlier studies in children. We used simple descriptive diagnostic criteria as well as discussion in a committee of three paediatric neurologists to determine whether the ictal event was epileptic or not. This method has been shown to increase the reliability of the diagnosis by reducing the

between rater variability.¹⁵ The origin of the ictal event was considered to be unclear in 51 children. During a one year follow up, only five (10%) of them developed epilepsy versus 72 (46%) of the children included with a first seizure. If we had diagnosed those five children correctly on admission and had not included children with a false positive diagnosis the recurrence rate at one year would in the worst case alter only slightly to 77 of 161 (48%). Because the much greater disadvantages of a false positive diagnosis a low number of false negative diagnoses is in our opinion preferable to inclusion of falsely positive diagnosed children. In the patients with a questionable description of the event, the EEG did not always contribute to the correct diagnosis, as only three out of eight disputable patients with an epileptiform EEG1 developed epilepsy within one year.

The overall recurrence rate of 54% at two years after a first unprovoked seizure found in this study is higher than in other recent prospective studies^{3 8 9} and in a recent meta-analysis.¹² Factors that may have increased the recurrence rate in our study are the withholding of antiepileptic drug treatment after the first fit, and the high diagnostic accuracy by the use of strict diagnostic criteria. Furthermore, 49% of the children were seen within 24 hours and 71% within one week. Therefore, the number of children who were not included because of an early recurrence, was probably small.

The risk factors for recurrence identified in this study were similar to those reported by others.¹² An EEG with epileptiform abnormalities proved to be the main risk factor for recurrence. Other factors associated with a higher risk of recurrence found in this study were remote symptomatic aetiology, or mental retardation, or both and abnormal CT. The children in whom no CT was carried out, had the lowest recurrence rate. Obviously, the neurologists selected children for CT on clinical grounds. In our opinion CT is not routinely indicated for children presenting with a first seizure.

Remarkably, whereas others have found that the occurrence of a first seizure during sleep is associated with an increased risk of recurrence,²² we found the opposite. We think that the use of strict criteria and discussion of each child by the expert committee lowered the number of children with non-epileptic events. Non-epileptic events are less likely to occur during sleep. This may have caused a bias in other studies.

Despite the relatively high recurrence rate, most children did well in the end. Our strategy to delay treatment after the first unprovoked seizure in our study group of 156 children led to a rather high recurrence rate of 54%. The long term outcome was poor in only 22 out of 156 children (14%) using terminal remission as the criterion. Many of the children with a poor outcome had infrequent generalised tonic-clonic or rolandic seizures, of which one or two coincidentally occurred during the final half year of the two year follow up. This

explains the better outcome in terms of longest remission ever.¹⁹

There is controversy over whether treatment should be offered after a single seizure. In Europe, children with single unprovoked epileptic seizures are usually not treated. The current clinical practice is to defer treatment until two or more seizures have occurred, although children perceived to be at high risk for recurrence may be treated after a single fit. The Italian First Seizure Trial Group carried out a controlled randomised trial of anticonvulsant therapy after a first generalised tonic-clonic seizure that occurred within the preceding seven days, in a large cohort including 113 children.¹¹ After two years, the recurrence rate for these children was significantly lower in the treated group (25% *v* 51%). Treatment after the first seizure did not, however, improve long term prognosis.²⁴

For an answer to the question whether treatment should be started in a child presenting with a first epileptic seizure, more knowledge of the long term outcome after recurrence is urgently needed. From our study, it may be concluded that the indication for starting long term anticonvulsant treatment after a single seizure in childhood is weak, because the risk of developing intractable epilepsy is already low. Immediate treatment will probably not further improve long term prognosis.²⁴ Treatment of all children after a single seizure therefore means treatment of many who will never have a second seizure; treatment of many whose epilepsy will have a benign course irrespective of treatment; and treatment of only a small minority in the hope of preventing them becoming intractable. Unfortunately, we are not able to predict which children will do badly after a single seizure. This would allow us to restrict treatment to these children. At this time, it seems to be advisable to delay long term anticonvulsant treatment until recurrent seizures are adversely affecting the child's life without signs of spontaneous remission. In so doing many children will never have to start long term treatment.

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