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Risk of recurrence after first unprovoked tonic-clonic seizure in adults

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Abstract The likelihood of seizure recurrence after a first unprovoked seizure has profound social, vocational and emotional implications for the patients. Recurrence rates have varied between 27% and 71% in various studies, and the management of patients with a single unprovoked seizure is a controversial topic. In this prospective study we investigated the influence of age, sex, family history, EEG patterns, and anticonvulsant drug (ACD) therapy on seizure recurrence after a first unprovoked tonic-clonic seizure in adults. For this purpose, between October 1988 and January 1991, we studied adult patients who had experienced their after unprovoked tonic-clonic seizure within last 2 months before neurological consultation, and followed them until June 1993. There were 147 patients who met the criteria for inclusion. Overall cumulative recurrence rates were 31.8% by 6 months, 41.3% by 1 year, 44.1% by 2 years, 42.2% by 3 years, and 45.2% by 4 years. Among the risk factors that were evaluated, the time of the day at which the initial seizure occurred was associated significantly ($P < 0.05$) with seizure recurrence. In our series, 62 patients received ACD and 85 did not. We did not find a significant difference in recurrence rate with regard to ACD therapy. Our results are comparable with those of studies reported preeviously and suggest that the majority of recurrences after a first unprovoked seizure were seen in the first year (in our series 89% of all recurrences). In our study there was no significant predictor of seizure recurrence, except the time of day at which the initial seizure occurred.

Key words Epilepsy · Seizure recurrence · Anticonvulsant therapy

Introduction

It has been suggested that up to 5.9% of the population will experience at least one non-febrile seizure at some stage of their life [6, 11]. The likelihood of seizure recurrence after a first unprovoked seizure has profound social, vocational and emotional implications for the patients [8].

When medical reports about prognosis after initial unprovoked seizures are reviewed it can be seen that there is not a sufficient body of knowledge about this subject. Recurrence rates have varied between 27% and 71% in different reports [1, 9, 13] and may be related to the differences in methodology (retrospective vs prospective), and such factors as the numbers of patients, age groups studied, duration of follow-up period, etc.

Epilepsy is a heterogeneous condition, and factors that may influence the risk of recurrence, such as age, seizure type, family history, electroencephalographic (EEG) pattern, anticonvulsant drug (ACD) therapy, or duration of follow-up should be monitored if comparisons between studies are to be made. The management of patients with a single, unprovoked seizure is a controversial subject.

The issue of whether or not to use ACD in the patients is still under debate [9].

This aim of our study was to investigate prospectively the influence of age, sex, family history, seizure type, EEG patterns and ACD therapy on seizure recurrence after a first unprovoked seizure and to compare our results with those in literature.

Patients and methods

Our study group consisted of outpatients who had experienced their first seizure between October 1988 and January 1991 and who were followed until June 1993. We included patients over 16 years old who had experienced their first idiopathic tonic-clonic seizure during the previous 2 months. Patients with simple or complex partial seizures and those who had structural lesions proven by computed tomography (CT) were excluded.

At the initial neurological consultation we collected the pertinent data on the family history of convulsions or seizures, a description of the first seizure, etc. If the seizure occurred between midnight and 9 a.m. it was considered to be a nocturnal seizure. We performed routine scalp EEG and cranial CT in all patients. We obtained EEGs during the interictal period, usually more than 48 h after the first seizure. All EEGs were evaluated by two of the authors (I. B. and S. S., who were unaware of the outcome) and were divided into four categories: (1) generalized spike and wave activity (GSW) (2) focal spike and wave, or slow wave activity (FSW); (3) non-specific slow wave activity (NSW), and (4) within normal limits.

ACD therapy had been recommended for 44 patients first treated by a neurologist from another centres. It was further recommended for 18 by one of us, in those considered to be at high risk of recurrence after the initial seizure. We did not change or discontinue the ACD therapy in the 44 patients of the former group, but only adjusted dosages to obtain therapeutic serum levels. In all patients who received ACD therapy, serum levels were investigated periodically.

Analysis

We investigated the differences in probabilities of recurrence between age, sex, time of first seizure occurrence, seizure type, EEG patterns, and ACD therapy. The cumulative risk of recurrence was determined by life-table methods with event defined as seizure recurrence. These methods take into account the length of the follow-up period in each individual. The results are presented as Kaplan-Meier survival curves representing the probability of remaining free from further seizures conditional on surviving the specified time interval (follow-up period) seizure-free. Univariate analysis was performed using the Kaplan-Meier "product limit method" and statistical significance was calculated using the method of Mantel-Haenszel [15]. For this analysis recurrence in patients with the factor questioned is compared with those without, irrespective of the presence of competing risk factors in either group. The proportional hazards model was used to estimate univariate and multivariate rate ratios, defined as the ratio of the rate of seizure recurrence in the group of patients with a given factor to the rate of recurrence in those without that factor. Findings were considered significant when the bounds of the 95% confidence interval did not include unity.

Table 1 Multivariate analysis of the risk of recurrence after a first unprovoked seizure (*CI* confidence interval; *GSW* generalized spike and wave, *FSW* focal spike and wave, *NSW* non-specific slow wave activity

Variable	*n*	Observed recurrences (%)	Odds ratio	95% CI
Total	147	63 (42.9)	–	–
Male	77	35 (45.5)	1.2	0.6–2.4
Age:				
16–20 years	45	23 (51.1)	1.6	0.7–3.3
21–40 years	81	31 (38.3)	0.6	0.4–1.5
> 41 years	21	10 (47.6)	1.2	0.4–1.3
Enuresis nocturna	28	12 (42.9)	1.0	0.4–2.4
Family history	17	8 (47.1)	1.2	0.4–3.6
Nocturnal seizure	63	34 (54.0)	2.1	1.0–4.3*
Primary generalized seizure	111	49 (44.1)	1.1	0.5–2.5
EEG patterns:				
GSW	39	15 (38.5)	0.8	0.3–1.7
FSW	12	4 (33.3)	0.6	0.2–2.4
NSP	31	13 (41.9)	0.9	0.4–2.2
Normal	65	32 (42.2)	1.5	0.7–3.1
ACD (–) patients	85	41 (48.2)	1.6	0.8–3.3

* Significant ($P = 0.028$)

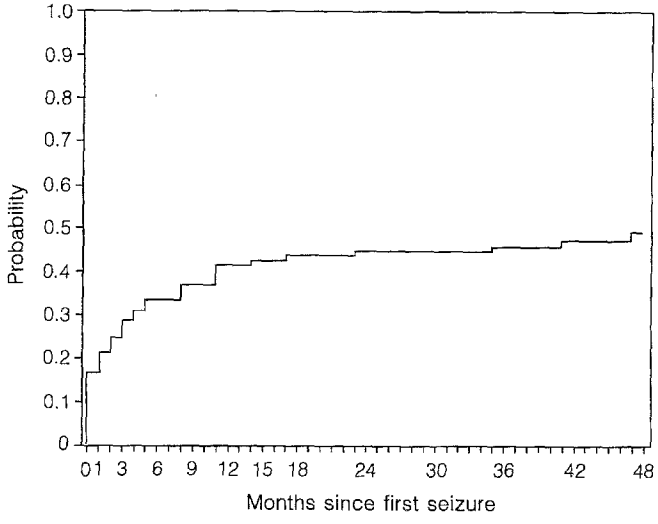

Fig. 1 Probability of seizure recurrence following first unprovoked seizure. Kaplan-Meier survival curve

Results

Our study was of 147 adult patients with a first idiopathic generalized seizure. The general characteristics of the study population are shown in Table 1. Briefly, 52.4%

Table 2 Probability of remaining free from seizures and risk of recurrence according to various factors. In each subgroup, numbers in the first row show patients at risk, in the second new recurrences, and in the third now probability of remaining free from further seizures. CI 95% = 95% confidence interval of odds ratio the percentage

	Cumulative time-dependent probability (%) of remaining seizure-free					
	6 months	12 months	24 months	36 months	Odd ratio	CI 95%
Total	147	108	97	41		
Recurrences	39	11	10	1	–	–
Probability (%)	68.2	58.7	55.9	54.8		
Male	77	55	48	22		
Recurrences	22	7	3	1	1.0	0.7–1.4
Probability (%)	74.1	67.5	64.9	62.0		
16–20 years	45	28	24	5		
Recurrences	17	4	2	0	1.6	0.8–3.0
Probability (%)	62.2	53.3	48.9	48.9		
21–40 years	81	60	54	26		
Recurrences	21	6	2	1	0.6	0.4–1.2
Probability (%)	74.1	66.7	64.2	61.7		
> 40 years	21	13	11	10		
Recurrences	8	2	0	0	1.1	0.7–.8
Probability (%)	61.9	52.4	52.4	52.4		
Enuresis nocturna	28	30	18	4		
Recurrences	8	2	2	0	1.2	0.8–2.0
Probability (%)	71.4	64.3	57.1	57.1		
Family history	17	13	13	2		
Recurrences	4	0	3	0	0.95	0.5–1.7
Probability (%)	76.5	76.5	58.8	58.8		
Nocturnal seizure	63	40	35	16		
Recurrences	23	5	6	0	1.9*	1.0–3.5
Probability (%)	60.3	49.2	46.0	46.0		
Primary generalized seizure	111	79	68	33		
Recurrences	32	11	4	0	0.9	0.6–1.4
Probability (%)	68.5	61.3	57.7	57.7		
GSW EEG	39	28	26	12		
Recurrences	11	2	0	1	0.7	0.5–1.1
Probability (%)	71.8	66.7	66.7	62.5		
FSW EEG	12	10	8	2		
Recurrences	2	2	0	0	0.8	2.4–1.6
Probability (%)	75.0	66.7	66.7	66.7		
NSW EEG	31	23	20	9		
Recurrences	8	3	2	0	1.0	0.6–1.6
Probability (%)	74.2	64.5	58.1	58.1		
Normal EEG	65	45	37	18		
Recurrences	20	8	3	0	1.5	1.0–2.1
Probability (%)	63.1	53.8	52.3	52.3		
ACD (–)	85	58	53	9		
Recurrences	27	7	7	1	1.6	0.9–3.0
Probability (%)	65.9	57.6	54.1	52.9		

* Statistically significant

were male and 47.6 female, ages varied from 16 to 66 years (mean 23.8), and patient numbers decreased with advancing age. In our study, 104 patients (70.7%) were admitted to our hospital within the first month (64 of them within first week), and 43 (29.3%) patients within the second month after the initial seizure. The follow-up period ranged from 27 to 54 months (mean, 34.4 months).

Overall recurrence rate was 14.3% by 1 month, 21.8% y 3 months, 31.8% by 6 months, 41.3% by 1 year, 44.1% by 2 years, 42.2% by 3 years, and 45.2% by 4 years (Fig.

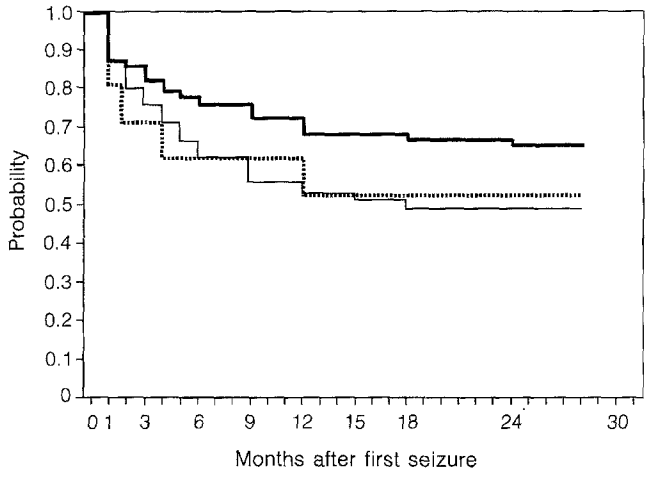

Fig. 2 Probability of remaining free from further epileptic seizures as a function of age. Kaplan-Meier curves. There is no significant difference between the curves — 16–20 years; — 21–40 years; ····· 41+ years

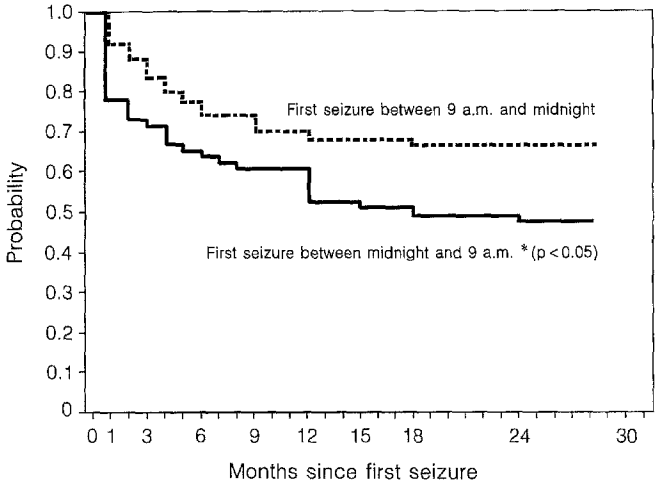

Fig. 4 Probability of remaining free from further epileptic seizures as a function of the time of day at which the first seizure occurred. Kaplan-Meier curves. Difference between the curves is significant ($P < 0.05$)

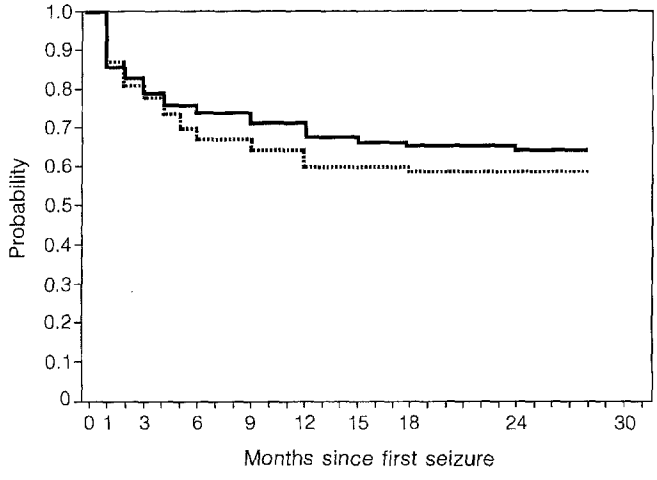

Fig. 3 Probability of remaining free from further epileptic seizures according to sex. Kaplan-Meier curves. There is no significant difference between the curves, — male; ····· female

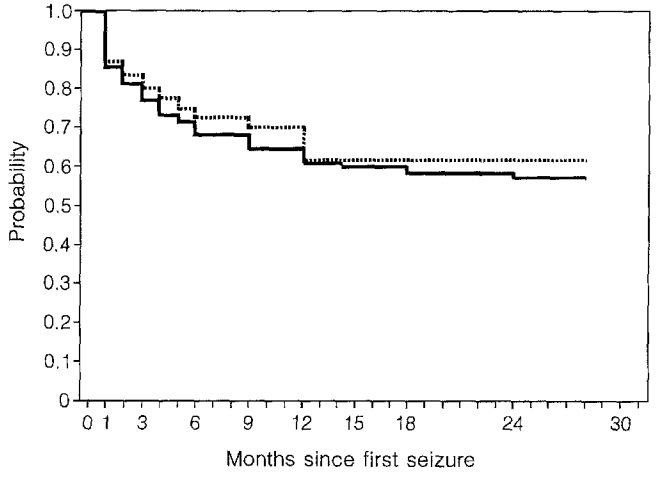

Fig. 5 Probability of remaining free from further epileptic seizures as a function of type of first seizure. Kaplan-Meier curves. Difference between the curves is not significant, — Primary generalized seizure; ····· Secondary generalized seizure

1). The risk of seizure recurrence was highest in the first year and tended to decrease with increasing time after the first seizure.

Recurrence rates were highest in those younger than 20 years; 38% at 6 months, 47% at 1 year, and 51% at 2 years. Within regard to the risk of recurrence, differences between age groups were not significant (Table 2, Fig. 2).

Recurrence rates for male patients were 32% at 1 year, 35% at 2 years, and 38% at 3 years, and were slightly higher than for females as of the 2nd year. Sex was not found to be a significant predictor of recurrence (Table 2, Fig. 3).

We also investigated certain clinical features that were considered to be associated with seizure recurrence; 28 of our patients (19%) have a history of enuresis nocturna and 17 patients (11.6%) have a family history in first-degree relatives. Ten of 12 recurrences in patients with a history of enuresis were seen within the first year after the initial seizure and the recurrence rate was 36% (Table 2). For those with a family history, recurrence rates were 24%, 24% and 41% at 1, 2, and 3 years respectively (Table 2). We did not find a significant difference between patients with or without a history of enuresis nocturna, or a family history.

As regards the time of day at which the first seizure occurred, 63 patients (43%) experienced the first seizure between midnight and 9.00 a.m. (nocturnal seizure), and 84 (53%) between 9.00 a.m. and midnight (daytime seizure). For a nocturnal first seizure recurrence rates were 40% at

Table 3 Subgroup analysis of the risk of recurrence after first seizure (CI 95% = 95% confidence interval of odds ratio; *RR* relative risk)

Variables	Enuresis nocturna		Family history		Nocturnal seizure		Primary generalized seizure	
	RR	CI 95%	RR	CI 95%	RR	CI 95%	RR	CI 95%
Male	1.1	0.5–2.6	4.9	0.8–31.5*	1.0	0.6–1.5	1.3	0.8–1.9
Age:								
16–20 years	2.1	1.0–4.6	0.6	0.2– 2.1	1.1	0.7–1.7	1.3	0.9–2.0
21–40 years	0.6	0.3–1.5	1.6	0.6– 5.7	0.9	0.6–1.4	0.9	0.6–1.3
>40 years	0.7	0.2–2.5	[a]	[a]	1.0	0.5–2.0	0.9	0.5–1.7
Enuresis nocturna	–	–	1.9	0.8– 4.7	0.6	0.3–1.4	0.6	0.3–1.4
Family history	2.0	0.9–4.3	–	–	1.3	0.7–2.4	1.3	0.7–2.2
Nocturnal seizure	0.8	0.3–2.0	1.8	0.7– 4.8	–	–	1.5	1.0–2.3
Primary generalized	0.5	0.2–1.1	2.1	0.4–12.6	1.1	0.7–1.9	–	–
EEG patterns:								
GSW	1.2	0.5–3.1	0.7	0.1– 3.6	0.8	0.4–1.4	0.9	0.5–1.5
FSW	0.8	0.1–4.0	[a]	[a]	0.7	0.2–2.1	2.3	1.9–2.8
NSP	1.0	0.4–2.7	1.6	0.6– 4.2	1.1	0.6–1.8	0.9	0.5–1.5
Normal	0.9	0.4–2.2	1.5	0.5– 4.3	1.3	0.8–2.0	1.1	0.7–1.7
ACD(–)	2.0	0.8–5.1	1.6	0.5– 5.7	1.3	0.8–2.1	1.5	0.9–2.4

* $P < 0.05$
[a] No analysis due to small number of cases in a subset of this category

6 months, 51% at 1 year, and 54% at 2–3 years (Table 2, Fig. 4). If the first seizure was a daytime seizure, recurrence rates were 24%, 30%, 32% and 33% at 6 months, 1, 2 and 3 years respectively. Risk of recurrence for nocturnal seizures is significantly higher ($P < 0.05$) than for daytime seizure (Table 2, Fig. 4).

In our series, the first seizure was a primary generalized tonic-clonic conclusion (GTC) in 111 patients (75.5%) and a secondary GTC in 36 (24.5%). Recurrence rartes at 6, 12, 24 and 36 months were 32%, 39%, 42% and 42% for primary GTC and 28%, 39%, 39% and 42% for secondary GTC respectively. The differences did not reach statistical significance (Table 2, Fig. 5).

To investigate the influence of additional factors on risk of recurrence cross-tables was analysed. In our study, except for male sex + family history (RR = 4.9, CI 95% = 0.8–31.5), a second factor did not increase the risk of recurrence significantly (Table 3).

EEG patterns were as follows: GSW in 39 patients (26%), FSW in 12 (8%), NSW in 31 (21%), and normal in 65 patients (44%). For those with GSW, recurrence rates at 6 months, 1, 2 and 3 years were 28%, 33%, 36% and 38% respectively (Table 2). For those with FSW, recurrence rates were 25% at 6 months, 33% at 1 year, and did not increase to the end of 4th year. Recurrence rates were 26%, 35%, 39% and 42% for the patients with NSW, and 37%, 46%, 48% and 49% for those with a normal EEG pattern. Risk of recurrence was higher in patients with normal EEG than in the others, but it did not reach statistical significance (Table 2, Fig. 6). In Table 4, subgroup analysis according to EEG pattern is shown; there was no significant difference in relative risks.

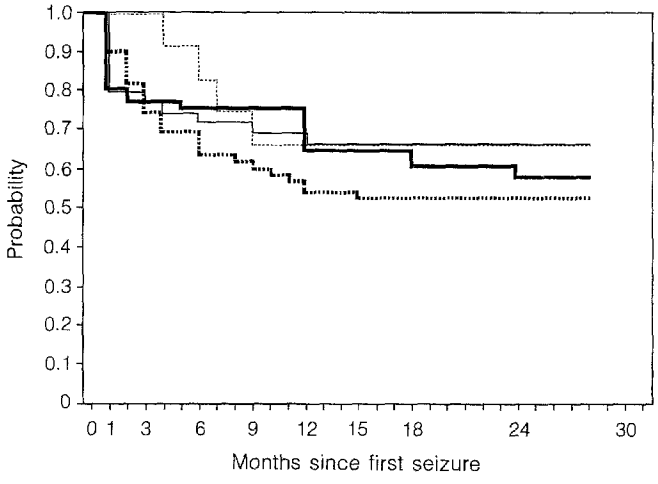

Fig. 6 Probability of remaining free from further epileptic seizures as a function of EEG pattern (*GSW* generalized spike and wave, *FSW* focal spike and wave, *NSW* non-specific slow wave activity). Kaplan-Meier curves. Differences between the curves are not significant, — GSW; ····· FSW; — NSW; ····· Normal EEG

In our series, ACD therapy was prescribed for 62 patients (42%) at the time of the first seizure. Recurrence rates at 6, 12, 24 and 48 months were 26%, 34%, 35% and 37% for those who received ACD therapy, and 34%, 42%, 46% and 48% for those who did not. Although the risk of recurrence during the follow-up period was higher for patients who were not receiving ACD therapy, there was not statistical significance (Table 2, Fig. 7).

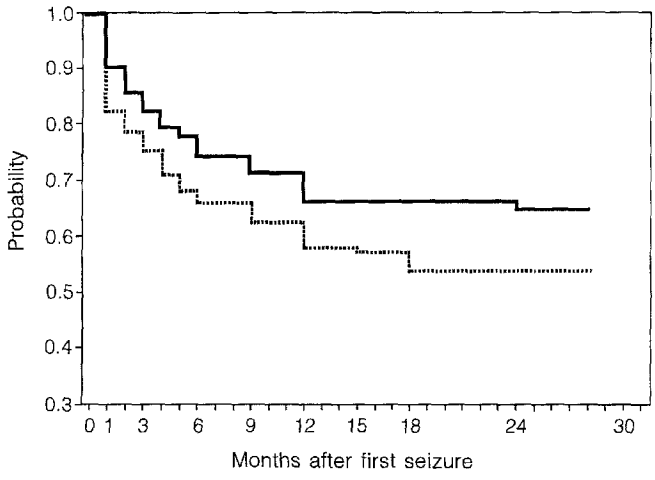

Fig. 7 Probability of remaining free from further epileptic seizures as a function of anticonvulsant drug (*ACD*) therapy. Kaplan-Meier curves. There is no significant difference between the curves. — ACD (+) patients; ····· ACD (–) patients

Discussion

More than 50% of newly diagnosed epileptic patients have experienced several convulsive episodes before receiving medical attention. In our study we did not include patients who had previously experienced multiple seizures.

The majority of individuals who experience a second seizure will do so in the first few months after the initial episode (and the majority of those who are at risk of having further seizures will be identified in a short time following the first event) [1, 10, 13]. In our study seizure recurrence was 31.8 in the first 6 months and 41.3% in the first year. Annegers et al. [1], in their series of 424 patients, found recurrence rates to be 30% by 6 months, 36% by 1 year and 56% by 5 years. In the study by Houser et al. [10] that comprised 244 patients with a first idiopathic seizure, the overall recurrence rate was 16% by 1 year and 27% by 3 years, and there were no recurrences among patients followed more than 3 years. Hopkins et al. [13] found the risk of recurrence to be 39% by 1 year and 52% by 3 years for patients seen within the first week after their initial seizure. In our series recurrence rates were 41.3%, 44.1% and 42.2% by the end of 1, 2 and 3 years respectively, and the cumulative recurrence rate was 45.2% for the follow-up period of 4 years.

The risk of recurrence after an initial seizure is greater in children than in adults. Hirtz et al. [12] found the recurrence rate to be 69% in children with non-symptomatic initial seizures. For some seizure types, such as absence, akinetic "minor motor", myoclonic and infantile spasms the recurrence risk is virtually 100% [2]. The recurrence rates after a single non-febrile generalized seizure have ranged between 25% and 75% in children [12], and despite ACD therapy, 41% had a recurrence within 6 months of starting treatment [3].

In various papers it has been stated that some factors such as seizure type, neurological deficits, family history and spike-and-wave activity on EEG influence the risk of recurrence after initial seizures. GTC seizures had the best prognosis (44% recurred); partial complex seizures recurred more often (79%) [2, 3, 14]. Hopkins et al. [13] reported that age, sex, family history, type of seizure, or EEG features were not of predictive value, and Hauser et al. [10] found that in patients with idiopathic seizures there were differences in the risk of recurrence depending on age, sex, seizure type, seizure duration or the abnormalities on neurological examination.

There has not so far been genaral agreement on the predictive value of EEG abnormalities. Various studies have reported abnormal EEGs to be predictive of recurrence: Cleland et al. [4] found a recurrence rate of 53% in patients with abnormal EEG findings including spike and

Table 4 Subgroup analysis of the risk of recurrence after first seizure according to EEG patterns (*RR* relative risk)

	GSW $n = 39$		FSW $n = 12$		NSW $n = 31$		Normal $n = 65$	
	RR	CI 95%	RR	CI 95%	RR	CI 95%	RR	CI 95%
Male	1.4	0.6–3.2	0.3	0.1–2.4	0.8	0.4–1.9	1.2	0.8–2.1
Age:								
16–20 years	1.7	0.8–3.8	2.1	3.5–15.1	0.6	0.2–1.6	1.7	1.1–2.6
21–40 years	0.7	0.3–1.7	0.7	0.1– 4.5	1.9	0.8–4.2	0.7	0.4–1.1
>40 years	1.8	0.7–4.6	[a]	[a]	0.5	0.2–1.9	1.1	0.6–2.1
Enuresis nocturna	1.4	0.6–3.5	1.0	0.2– 6.4	1.0	0.4–2.7	0.8	0.4–1.7
Family history	0.9	0.2–4.5	[a]	[a]	1.7	0.7–4.3	1.1	0.6–2.2
Nocturnal seizure	1.3	0.6–2.8	1.4	0.3– 6.9	2.1	0.8–5.4	1.5	0.9–2.4
Primary generalized	1.2	0.5–3.1	3.7	1.4– 9.6	0.8	0.3–2.4	0.7	0.4–1.2
ACD(–)	1.3	0.6–2.9	1.0	0.2– 4.9	1.2	0.4–3.2	1.0	0.6–1.7

* $P < 0.05$
[a] No analysis due to small number of cases in a subset of this category

wave or non-specific slowing, compared with 26% in patients with a normal EEG. Hauser et al. [10] reported that the risk of recurrence in patients with a generalized spike and wave pattern on EEG was more than double that of patients with normal EEG (50% vs 14% at 24 months). Annegers et al. [1] and Camfield et al. [2] reported that focal abnormalities on EEG were found to indicate an increased risk of recurrence after the initial seizure. Shinnar et al. [16] reported 23% recurrences in children with idiopathic seizures and normal EEG, and approximately 50% in patients with abnormal EEG (by the end of a 2-year follow-up period), and stated that the EEG is the one of the key indicators of recurrence risk. In the present study, correlation between risk. In the present study, correlation between risk of seizure recurrence and EEG abnormalities in the whole study population did not reach statistical significance.

It appears to be the current practice of most neurologists not to treat a single seizure [9]. Hauser et al. [10] found no differences in recurrences rates between treated and untreated patients with idiopathic seizures. ACD therapy could be recommended to patients considered to be at high risk of recurrence [5]. On the other hand, a single seizure in an intact patient with normal test results suggests a more conservative approach [7]. If a seizure is associated with a structural lesion and epileptogenic activity on EEG, although there is a 30% risk of side effects, ACD therapy may be initiated [7]. In our study, the risk of recurrence in untreated patients was higher than in treated ones (OR = 1.6, CI 95%: 0.8–3.3), but not significantly. It has been reported that remission was usually achieved within 12 months of starting treatment [14, 17]. Prognosis is worse in patients that have recurrent seizures within the first 12 months when compared with seizure-free patients during the same period [4]. Although recurrences are possible years after the initial seizure, the risk of recurrence is higher int he first few months; therefore, the first 6 months after the initial seizure can be highly predictive as regards the prognosis of patients with idiopathic seizures.

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