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Original Article

Seizure recurrence after a first unprovoked seizure: With and without treatment

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Abstract

BACKGROUND: Most of the studies have shown that approximately one third of patients with single seizure will experience a second one. Data regarding seizure-free survival time and recurrence rate vary widely. We investigated the likelihood of a second attack and seizure-free survival time with and without early treatment in our epileptic patients.

METHODS: Patients of the first unprovoked seizures were recruited between 2000-2005 years. They were randomized into two groups: one treated with carbamazepine and the other was not treated. After obtaining a written consent, all patients were followed up for a second seizure for a period ranging from 12 to 36 (19.1 ± 5) months.

RESULTS: A total number of 150 patients were enrolled in this study, of which 13 patients were lost to follow up. The remaining patients (71 males and 66 females) were followed up during 5 years. They were randomized into two groups: treatment (50 patients) and non-treatment (87 patients); 30.2% of all patients were without relapsing, of which 48.9% were on treatment (case) and 19.5% did not receive any treatment (the control group). The mean seizure-free survival times were 6 months and 3.8 months in the treated and non-treated patients, respectively ($P = 0.017$).

CONCLUSIONS: We found strong correlation between relapse and treatment started after the first attack ($P < 0.05$); i.e., the patients who received treatment in their first attack may be at lower risk of relapsing.

KEY WORDS: Unprovoked seizure, first seizure, recurrence, treatment, survival time.

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Many individuals who experience a first unprovoked seizure never experience a second one. By definition, these people do not have epilepsy and generally do not require long-term therapy. Unfortunately, our ability to identify such individuals with accuracy is incomplete.[1] The incidence of single seizure in general population is 5%, whereas epilepsy develops in 1-2% of them. A single seizure does not constitute epilepsy, which is defined as occurrence of at least 2 episodes of unprovoked seizures.[2] Most of the studies have shown that approximately one third of patients with single seizure will experience a second one. [3,4] Prospective studies of recurrence after a first seizure indicate a 2-year recurrence risk of about 40%, which is similar in children and adults.[5] About 25% of patients with unprovoked seizures come to a neurologist after a single attack.[6] Data regarding recurrence of seizure is varying widely. It has been reported that recurrence rate is between 58-80% in these patients.[7,8] In a prospective study, Hauser et al estimated the risk of recurrence to be 14%, 29% and 34% at 1, 3 and 5 years, respectively, following the first episode. Although treatment of first seizure reduces the relapse rate even in low-risk patients, there is no evidence that such treatment alters the prognosis of epilepsy.[9] Thus,

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treatment should not be started automatically, and the decision for treat should be made only in consultation with the patient or parents after weighing the unique circumstances posed by the individual. In most patients with idiopathic epilepsy, deferring of treatment until the occurrence of a second seizure might be a reasonable and often preferable decision.[10] There is a wide variation both in the reported prognosis after a first unprovoked generalized tonic-clonic convulsion, and in the risk factors that are associated with recurrence. It is estimated that the risk of recurrence ranges from 26 to 71%.[11] Uncertain occurrence of a second attack after the first seizure, controversial treatment of the first unprovoked seizure, side effects of anti-epileptic drugs, and lack of these surveys in our patients necessitated doing the present study. However in patients with a single epileptic seizure or rare seizures, the decision to treat or not to treat requires careful consideration of risk to benefit ratio. This is primarily dependent on the probability of seizure recurrence in the absence of treatment, and the impact of treatment on such probability. We investigated the likelihood of a second attack and survival time of being seizure-free in our epileptic patients.

Methods

This was a clinical trial of adult patients with first idiopathic generalized seizures; 150 patients of single unprovoked generalized seizure were recruited from the neurology department of Al-Zahra Hospital of Esfahan University of Medical Sciences, between 2000 and 2005. Patients with a history of provoked seizure, symptomatic etiologies (occupying space lesions, trauma, stroke, infection, etc.) presence of focal neurological deficit, definite abnormal EEG and positive family history were also excluded. Age, sex, type of seizure, time of the occurrence of ictus, interval between onset and referral, and family history of seizure in first degree relatives were recorded. All the patients were subjected to EEG and brain CT scan and MRI. The patients were interviewed along with one attendant and were explained the risks and benefits of anticonvulsant therapy as well as that treatment of a single seizure is controversial. The patients were randomly divided into two groups (case and control). The case group immediately received monotherapy with carbamazepine (10-30 mg\kg) for 12 months if the relapse did not occur. The control group received no treatment but they were asked to give a written consent. All patients were followed up for recurrence at monthly intervals for 3 months, then quarterly for 1 year and once in 6 months thereafter, for a period ranging from 12-36 months (mean, 19.1 ± 5). In the case of occurring relapse, the exact time was registered for both groups. The seizure-free survival time of the two groups was also detected. The duration between the first and the second seizures and the time interval between them were intended to be the probable outcome of this study. The data were analyzed by the chi-square test. P values were calculated and compared in the group having recurrence of seizure versus those without recurrence. The results of recurrences were statistically analyzed by using the Kaplan-Meier method and log rank test.

Results

One hundred and fifty patients were enrolled in this study and 13 patients were lost to follow up either due to no recurrence or no cooperation. The remaining patients included 71 males and 66 females who were followed up during 5 years. The two groups (case or treatment and control or non-treatment) included 50 and 87 individuals, respectively. The average age of patients in the case group and the control group was 31.4 ± 17 and 28 ± 15 years, respectively. The comparisons of the other variables such as sex, marriage, job and education of the two groups were not significant (P > 0.0.5, table 1). About 30.2% of all patients were without relapsing; among of them 48.9% and 19.5% were on treatment (case) and no treatment (control), respectively. Around 69.8% of all patients had recurrent seizures; 51.1% of them were on treatment and 80.5% had no treatment (table 1). The comparisons of the two

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groups were statistically significantly (P < 0.001). The mean seizure-free survival times were 6 months and 3.8 months in the treated and non- treated patients, respectively (P = 0.007, table 2). The seizure-free survival time between the two groups was tested by Log-Rank test and it was statistically significant (figure 1).

Table 1. The frequency of distribution of sex, marriage status and relapse seizure between the two groups.

Group Variables		Treatment		Control		Total		P
		N	%	N	%	N	%	
Sex:	Male	27	54	44	50.6	71	51.8	>0.05
	Female	23	46	43	44.9	66	48.2	
Marriage:	Married	22	48.9	41	54.7	63	54	>0.05
	Single	23	51.1	34	45.3	57	46	
Relapse:	No	23	48.9	16	19.5	39	30.2	<0.001
	Yes	24	51.1	66	80.5	90	69.8	

Table 2. The seizure-free survival times in the two groups.

Group	Treatment*	Control
Number of Relapses	24	36
Lost to Follow up	3	10
Seizure-free Survival Time (Months) †	6 ± 0.32 (3.1-4.4)	3.8 ± 0.99 (4.1-7.97)
Seizure-free Survival Time (Months) ‡	3, 0.48 (2.1-3.9)	4, 0.51 (3-4.99)

* P < 0.05
† Mean ± SE (95% CI)
‡ Median, SE (99% CI)

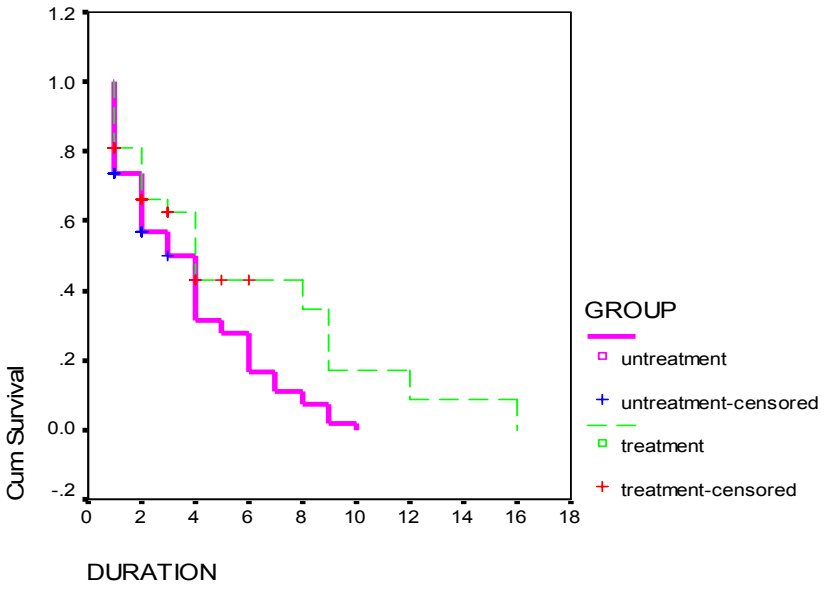

Figure 1. Comparison of the seizure-free survival times in patients with and without treatment.

Discussion

This study was the first report addressing the likelihood of recurrence of the first seizure and the seizure-free survival time for a second attack in our population. An epileptic seizure is the result of a temporary physiologic dysfunc-

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tion of brain caused by a self-limited abnormal, hyper-synchronous electrical discharge of cortical neurons.[12] Treatment decisions must be based on epidemiologic and individual considerations. The relapse rate of some seizure types, such as absence and myoclonic seizures, are virtually highest. The risk is lowest in people with first idiopathic generalized seizure and normal EEG (about 24%), higher with idiopathic generalized seizures and an abnormal EEG (about 48%), and highest with symptomatic seizures and an abnormal EEG (about 65%). If the first seizure is a partial seizure, the relative risk of recurrence will also be increased.[10,13] Our patients had single unprovoked generalized seizures with or without normal EEG but their neurological examinations were normal. Their neuroimaging and other tests were normal as well. In the series reported by Cleland and colleagues, the risk of another seizure over 10 years was 13 percent unless the first episode was status epilepticus, in which case the risk was 41 percent. Age, sex, and the circumstances of the seizure (withdrawal from drugs or alcohol, myoclonic episodes, family history, etc.) all figured into the risk.[14] It has been our practice to administer an anticonvulsant and to re-evaluate the situation in a matter of 6 to 12 months, with the goal of eventually discontinuing the medication. This approach has been prompted by data such as that of Hauser and colleagues, who found that about one-third of patients with a single unprovoked seizure will have another seizure within 5 years. The risk is even greater if there is a history of seizures in a sibling, a complex febrile convulsion in childhood, or a spike-and-wave abnormality in the EEG. Moreover, the risk of recurrence is greatest in the first 24 months. [4,15] Gilad et al study on 87 patients after 3 years showed seizure-free survival time of patients on early treatment was longer than that in control group ($P = 0.001$) and this result was more substantial in males than in females.[16] Other clinical trials reported most recurrent seizures occur in the first 3 months.[17] Anticonvulsant therapy in children reduced the risk of seizure relapse about 50% in the first 3 months and its effect diminished later on the next relapses.[18] Also, the type of drug and the dosage were effective in the prevention of seizure relapses. However, some surveys have not shown significant results, probably because of differences in their design and inclusion criteria.[19] In addition, some of them reported mild increase in the rate of relapses in spite of treatment.[20] The determination of seizure-free survival times and relapsing rates were the important aims of our study. About 70% of the patients had recurrent attacks and 30% did not have relapses. The recurrent attacks were seen in both groups but they were higher in the group without treatment ($P < 0.001$). The mean seizure-free survival time in the treatment group was 6 months and in the group without treatment was 3.8 months. Log rank test showed the difference of survival time in the two groups was statistically significant. Finally, we found significant decrease in relapse rate and prolonged seizure-free survival time after the first seizure in the patients with early treatment. In other words, with treatment a number of patients relapsed so that treatment can't guarantee seizure freedom.

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