

RISK OF RECURRENT SEIZURES AFTER TWO UNPROVOKED SEIZURES

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ABSTRACT

Background Patients with a single unprovoked seizure have about a 35 percent risk of recurrence in the subsequent five years. We studied the risk of recurrence after two unprovoked seizures.

Methods We prospectively followed 204 patients with a first unprovoked seizure from the day of the initial seizure. Information was obtained from patients (and verified by a review of their medical records) about the dates and circumstances of any subsequent seizures. The risk of a second, third, and fourth seizure was estimated by the Kaplan–Meier method.

Results Of the 204 patients, 63 had a second seizure, 41 a third seizure, and 26 a fourth seizure. The mean age of the patients was 36 years, 10 percent were less than 16 years of age, 70 percent were male, 71 percent had epilepsy of unknown cause, and 66 percent had generalized seizures. The risk of a second unprovoked seizure was 33 percent. Among those with a second seizure, the risk of a third unprovoked seizure was 73 percent; among those with a third unprovoked seizure, the risk of a fourth was 76 percent. Most recurrences occurred within one year of the second or third seizure. The risk of a third seizure was higher in those with a presumed cause of epilepsy (relative risk, 1.9; 95 percent confidence interval, 1.0 to 3.4).

Conclusions Although only about one third of patients with a first unprovoked seizure will have further seizures within five years, about three quarters of those with two or three unprovoked seizures have further seizures within four years. (N Engl J Med 1998;338:429–34.)

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MANY studies have examined the risk of recurrence of seizures.¹⁻¹² The wide variation found in the risk of recurrence among those who have had a first seizure seems to be explained by differences in study design or differences in the characteristics of the study groups. Overall, about 35 percent of patients with a first seizure can be expected to have a second within the subsequent three to five years, although the risk varies from less than 20 percent to 100 percent, depending on clinical characteristics.²⁻⁴

The majority of those with newly recognized epilepsy have many seizures before diagnosis.^{1,2} Often, repetitive symptoms are necessary to establish a diagnosis; moreover, close temporal proximity of sequential seizures may be the reason patients seek medical care. The temporal patterns of seizure oc-

currence reported in patients with newly diagnosed epilepsy are generally reconstructed after the diagnosis has been made. They provide an inaccurate picture of the relation between patterns of previous seizures, the likelihood of further seizures, and the ultimate prognosis.^{1,3} It is more informative to study patients from the time of the initial seizure to determine the frequency and timing of further seizures.

We addressed the question of the risk of a third and a fourth seizure among patients who had had a second unprovoked seizure. We also evaluated the role of potential risk factors for recurrence. All the patients were followed prospectively from the date of their first unprovoked seizure.

METHODS**Patients**

A surveillance system, based on review of hospital admissions and referrals to electroencephalography (EEG) laboratories and neurology and epilepsy clinics at four hospitals affiliated with the University of Minnesota, was established to identify patients who were evaluated because of newly identified seizures. A total of 1157 such patients were identified.

Once their informed consent was obtained, the patients were screened to determine their eligibility for a series of studies. Interviews were scheduled to obtain a medical (especially neurologic), family, and social history. The interview, which required up to three hours, often could not be completed at the time of hospitalization, in which case it was scheduled after discharge.

Excluded from the study were 382 patients who had only acute symptomatic seizures (seizures occurring in close temporal association — generally within one week — of an acute insult to the central nervous system or seizures occurring at the time of an acute systemic metabolic or toxic insult)^{14,15} and 432 patients who had had multiple seizures before their first medical evaluation. A total of 343 subjects remained who had had a first unprovoked seizure. Eligibility for this study was restricted to the patients who at the time of the initial evaluation had had a definite unprovoked seizure, documented by an eyewitness; had no evidence in the history of a previous unprovoked seizure; were identified and signed informed-consent forms within 24 hours of the initial seizure; and completed the interview within 30 days of the initial seizure. Altogether, 271 patients were seen and recruited on the day of the index seizure. For 67 of these patients, the intake interview was not completed within 30 days. The remaining 204 patients were included in the analysis.

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Classification of Seizures

All seizures were categorized as partial or generalized on the basis of the description of the onset of the seizure by an eyewitness, according to criteria recommended by the International League against Epilepsy.^{16,17} Seizures were categorized according to the witness's description, without regard to the findings on EEG or the neurologic examination.^{14,16}

Each patient's seizure was also categorized as idiopathic or cryptogenic (seizures occurring in the absence of a documented insult that was thought to increase substantially the risk of unprovoked seizures) or as remote symptomatic (seizures in persons with a history of insult to the central nervous system that was known to increase substantially the risk for subsequent epilepsy, such as head trauma,¹⁸ cerebrovascular insult,¹⁹ central nervous system infection,²⁰ or static encephalopathy from birth, manifested by mental retardation or cerebral palsy,²¹ but not closely associated in time with the known or presumed cause). An unexplained localized abnormality identified in the diagnostic evaluation (e.g., a reflex asymmetry on examination or focal slowing on EEG) did not modify this categorization but was treated as a potential confounder in the analysis. In those with a first unprovoked seizure, information was collected for each subsequent seizure, thus potentially allowing reclassification of the seizure according to type or cause. Persons with status epilepticus (seizures continuing for 30 minutes or more without interruption) or clusters of seizures (two or more) in the same 24-hour period were considered to have had a single seizure. This was an observational study, and we made no attempt to influence the practice of the treating physicians once patients had been identified. Thus, there was neither standardization of treatment (if any) nor systematic monitoring of the adequacy of therapy in patients for whom antiseizure medication was recommended.

Follow-up

Subjects were contacted by telephone at six-month intervals for two years from the date of the first seizure and annually thereafter. Data collected included the date, duration, and clinical characteristics of any subsequent seizures, potential precipitating events, concurrent and previous use of antiseizure medication, and the details of neurologic insults, if any, since the previous follow-up contact. The medical records of those who reported additional seizure activity were reviewed to document the occurrence of seizures and to confirm reported medication use and obtain blood levels of medication, if available. The medical records generally confirmed the recurrence of seizures but seldom provided specific information on the type, frequency, or specific dates of seizures. Thus, the information used in our analysis came primarily from the interviews with patients. The medical records of those who did not report additional seizures were also reviewed periodically for other reasons, and no additional patients with seizures were identified. Follow-up was terminated for any of the following reasons: death, the occurrence of an event associated with an increased risk of unprovoked seizures (e.g., head injury with loss of consciousness or cerebrovascular insult), or a decision by the patient to end his or her participation in the study. Data were obtained on each seizure through the fourth episode. All protocols were approved by the institutional review board of the University of Minnesota.

Statistical Analysis

To determine the risk of a third unprovoked seizure, subjects who had had two unprovoked seizures were entered into the analysis on the date of the second such seizure and were followed until the date of the third or the end of follow-up. A similar strategy was used to evaluate the risk of a fourth unprovoked seizure after a third. Seizures were classified according to type and cause on the basis of the most recent data. The cumulative risk of recurrence after a second and a third unprovoked seizure was determined by Kaplan–Meier methods, with an “event” defined as a

recurrence of unprovoked seizures.^{22,23} These methods take into account the length of follow-up for each patient. The computed risks, therefore, represent the risk of recurrence among surviving patients. Univariate analysis (illustrated by Kaplan–Meier survival curves) for each variable estimated the cumulative risk of recurrence in relation to time after the index seizure.²⁴ All P values are two-tailed.

The proportional-hazards model was used to estimate univariate rate ratios, defined as the ratio of the rate of recurrence of seizures in the group of patients with a given factor to the rate of recurrence among those without that factor (e.g., the risk among patients with remote symptomatic seizures as compared with that among patients with idiopathic seizures).²⁵ All statistical analyses were performed with use of Stata software.²⁶ The reference group for all comparisons consisted of patients with an idiopathic or cryptogenic seizure. Age was analyzed as both a continuous and a discrete variable. Differences were considered significant when the bounds of the 95 percent confidence interval did not include 1.

RESULTS

Risk of a Third Unprovoked Seizure

Of the 204 patients who were eligible for analysis, 63 had a second seizure and 41 a third seizure (Table 1). The risk of a second unprovoked seizure within five years of the first seizure was 33 percent (95 percent confidence interval, 26 to 40 percent) (Table 2). There were no losses to follow-up or other withdrawals among those who had a second seizure; all were followed either until they had a third seizure or until the end of the study. Among the 63 patients who had two unprovoked seizures, the risk of further unprovoked seizures was 32 percent at three months after the second (95 percent confidence interval, 21 to 43 percent), 41 percent at six months (95 percent confidence interval, 29 to 53 percent), 57 percent at one year (95 percent confidence interval, 45 to 70 percent), and 73 percent at four years (95 percent confidence interval, 59 to 87 percent) (Fig. 1). The patients who had not had a recurrence within four years after a second seizure had no further seizures; they were followed, on average, for an additional three years.

Among the 37 patients classified as having idiopathic or cryptogenic epilepsy who had a second seizure, the risk of a third seizure was 64 percent at five years. Among the 26 subjects classified as having remote symptomatic epilepsy, the risk of a recurrence was 87 percent at five years. The univariate rate ratio for recurrence among these latter patients, as compared with those with idiopathic epilepsy, was 1.9 (95 percent confidence interval, 1.0 to 3.4). The recurrences in people with symptomatic epilepsy tended to occur sooner after the second seizure than was the case for those with idiopathic epilepsy (Fig. 2). In the univariate analysis, none of the following were associated with the risk of recurrence: seizure type, findings on EEG, neurologic findings, history of a previous acute symptomatic seizure, history of Todd paralysis (hemiplegia or monoplegia lasting from a few minutes to several days after an epileptic sei-

TABLE 1. CHARACTERISTICS OF 204 PATIENTS WITH UNPROVOKED SEIZURES.

VARIABLE	FIRST SEIZURE	SECOND SEIZURE	THIRD SEIZURE
No. of patients	204	63	41
Mean age — yr	36	34	33
Age <16 yr — no. (%)	20 (10)	5 (8)	4 (10)
Male sex — no. (%)	142 (70)	49 (78)	30 (73)
Type of seizure — no. (%)			
Generalized	134 (66)	42 (67)	27 (66)
Partial	67 (33)	21 (33)	14 (34)
Unclassified	3 (1)	0	0
Etiologic category — no. (%)			
Idiopathic or cryptogenic	145 (71)	37 (59)	20 (49)
Remote symptomatic	59 (29)	26 (41)	21 (51)
Status epilepticus — no. (%)*	18 (9)	7 (11)	5 (12)
Todd paralysis — no. (%)*	37 (18)	16 (25)	9 (22)
Median time to recurrence — mo	35.5	8.6	4.5
Maximal follow-up — mo	100.4	111.7	70.2
Antiseizure medication — no. (%)†			
No	53 (26)	8 (13)	4 (10)
Yes	151 (74)	55 (87)	37 (90)
Phenytoin	114 (75)	44 (80)	29 (78)
Phenobarbital	29 (19)	9 (16)	7 (19)
Carbamazepine	4 (3)	1 (2)	0
Other	4 (3)	1 (2)	1 (3)
Compliance with medication — no. (%)†			
Drugs taken as prescribed	69 (46)	21 (38)	10 (27)
Some taken, not all	11 (7)	9 (16)	8 (22)
None taken	56 (37)	14 (25)	9 (24)
Unknown ("don't remember")	15 (10)	11 (20)	10 (27)

*The numbers and percentages shown are for those with this condition at the time of the first seizure.

†The percentages shown are of all patients for whom medication was prescribed.

zure), family history of epilepsy, age at the time of the first unprovoked seizure, sex, history of multiple seizures or status epilepticus at the first episode of unprovoked seizure, prescription of antiepileptic medications at the time of the first unprovoked seizure, and length of time between the first and second seizures (≥ 6 months vs. < 6 months).

Risk of a Fourth Unprovoked Seizure

The 41 patients with a third seizure were followed until they had a recurrent seizure or until the termination of the study. Twenty-six (63 percent) had a fourth seizure. The risk of a fourth unprovoked seizure was 31 percent at three months (95 percent confidence interval, 16 to 46 percent), 48 percent at six months (95 percent confidence interval, 32 to 64 percent), 61 percent at one year (95 percent confidence interval, 44 to 77 percent), and 76 percent at three years (95 percent confidence interval, 60 to 91 percent) (Fig. 1). Among those remaining seizure-free three years after the third seizure (who were followed, on average, for an additional three years), no further seizures occurred.

Unlike the risk of recurrence after a first and a second unprovoked seizure, the risk of recurrence within four years after a third unprovoked seizure was the same among those with remote symptomatic epilepsy (76 percent) and those with idiopathic epilepsy (76 percent). Of factors tested as predictors of a fourth seizure, only Todd paralysis was associated with a significantly higher risk. The rate of recurrence among the 9 patients with Todd paralysis was 87 percent, as compared with 73 percent among the 32 without Todd paralysis (relative risk, 2.6; 95 percent confidence interval, 1.1 to 6.2).

Timing of Recurrence

For the three groups with first, second, and third unprovoked seizures, the majority of recurrences occurred in the first year after the index seizure (Table 2). Among those with a first seizure, 21 percent had a recurrence during the first year after the index event, and an additional 12 percent had a recurrence during the subsequent four years. Among those with two seizures, 57 percent had a recurrence within one year, and an additional 16 percent in the subsequent four years. Among those with three seizures, 61 percent had a recurrence within one year, and an additional 15 percent in the subsequent four years. The risk of recurrence in the subsequent four years for those who remained free of seizures for one year after the index seizure was 14 percent after the first seizure, and approximately 38 percent after the second or third seizure (Table 2). The risk of further seizures in the subsequent three years among those remaining seizure-free for two years after the index seizure was 7 percent after the first seizure, 31 percent after the second seizure, and 25 percent after the third seizure (Table 2). In the analysis of recurrence according to the length of time without seizures, the risk of additional seizures was greater after multiple seizures than after single seizures.

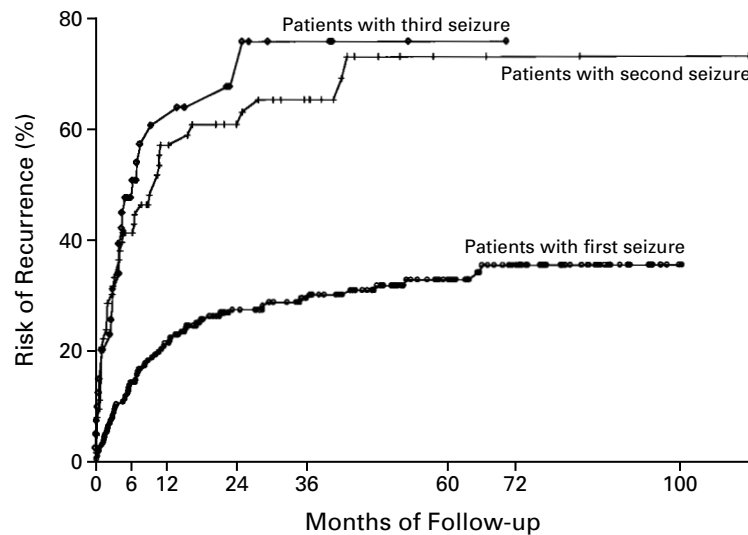
DISCUSSION

Unlike the relatively small risk of recurrence after a first unprovoked seizure (33 percent in five years), we found a substantial risk of additional seizures among persons with two or more unprovoked seizures. Our data suggest that roughly three quarters of those who have two or three unprovoked seizures will have additional unprovoked seizures within four years after the second or third unprovoked seizure. Not only is the risk of recurrence higher, but the recurrences are likely to occur within a shorter time, usually within a year of the second or third seizure. The risk of a third unprovoked seizure was higher among those with a history of neurologic insult (and thus with remote symptomatic epilepsy) than among those with no obvious antecedent (i.e., with idiopathic or cryptogenic epilepsy) (Fig. 1). The cause of the seizures did not predict the risk of recurrence

TABLE 2. RECURRENCE OF SEIZURES AT VARIOUS TIMES AFTER THE INDEX SEIZURE AND ACCORDING TO THE SEIZURE-FREE INTERVAL.*

VARIABLE	FIRST SEIZURE	SECOND SEIZURE	THIRD SEIZURE
No. of patients	204	63	41
percent with recurrence (95% confidence interval)			
Within 12 mo	21 (16–27)	57 (45–70)	61 (44–77)
Within 24 mo	27 (21–34)	61 (48–73)	67 (51–84)
Within 36 mo	29 (23–36)	65 (53–78)	76 (60–91)
Within 48 mo	32 (25–38)	73 (59–87)	76 (60–91)
Within 60 mo	33 (26–40)	73 (59–87)	76 (60–91)
No. of patients seizure-free for 12 mo after index seizure	153	24	12
percent with recurrence (95% confidence interval)			
Within 12 mo	8 (3–12)	8 (0–20)	17 (0–40)
Within 24 mo	10 (5–15)	19 (2–36)	38 (8–68)
Within 36 mo	13 (7–19)	37 (11–62)	38 (8–68)
Within 48 mo	14 (8–21)	37 (11–62)	38 (8–68)
No. of patients seizure-free for 24 mo after index seizure	117	19	8
percent with recurrence (95% confidence interval)			
Within 12 mo	3 (0–6)	11 (0–26)	25 (0–55)
Within 24 mo	6 (1–11)	31 (6–58)	25 (0–55)
Within 36 mo	7 (2–13)	31 (6–58)	25 (0–55)

*The percentages shown represent the risk of recurrence during the specified number of months after the first, second, or third unprovoked seizure.



PATIENTS AT RISK							
With first seizure	204	176	153	117	100	60	42
With second seizure	63	36	24	19	13		
With third seizure	41	18	12	8	4		

Figure 1. Risk of a Second, Third, and Fourth Unprovoked Seizure after a First, Second, and Third Unprovoked Seizure.

P<0.001 for the comparison of the risk after one seizure with the risk after two seizures. P=0.47 for the comparison of the risk after two seizures with that after three seizures. The numbers below the figure show the numbers of patients remaining alive and free of seizures.

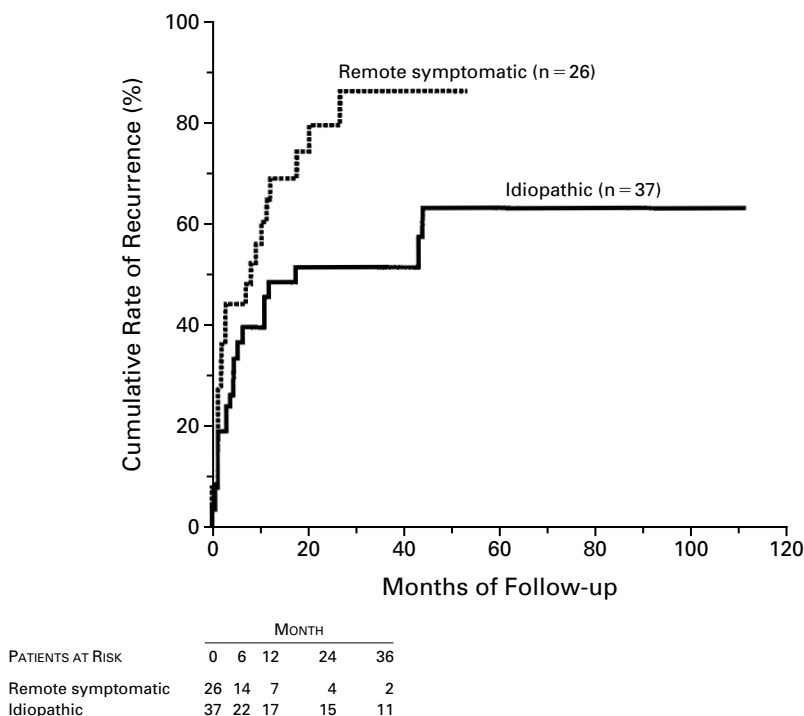


Figure 2. Risk of a Third Unprovoked Seizure after a Second Unprovoked Seizure in Patients with Remote Symptomatic Epilepsy and Idiopathic Epilepsy.

See the text for definitions. $P=0.05$ for the difference between the groups. The numbers below the figure show the numbers of patients remaining alive and free of seizures.

after a third unprovoked seizure. Todd paralysis was associated with an increased rate of recurrence. This observation is difficult to explain on a physiologic basis and requires confirmation in further studies. No other factors were identified as significant predictors of additional unprovoked seizures after a second or a third unprovoked seizure, although the statistical power of our study to identify such factors was limited.

Epilepsy is generally defined as a condition characterized by recurrent unprovoked seizures. In practice, there has been no agreement on an absolute number of seizures required for them to be considered recurrent. A few researchers have defined the term “epilepsy” to include patients with a single seizure,²⁷⁻²⁹ and a few have required three unprovoked seizures.^{30,31} Most recent clinical and epidemiologic studies have required two unprovoked seizures as a minimal criterion for the diagnosis.^{16,31} The international classification of epileptic syndromes proposed by the International League against Epilepsy categorizes patients with only a single convulsive episode separately from those with more than one seizure.³² The relatively low risk of further seizures among persons with a single unprovoked seizure contrasts

sharply with the higher risk after two or more unprovoked seizures. In our view, two unprovoked seizures are a necessary and sufficient criterion for the diagnosis of epilepsy.

Our data suggest that decisions about the nature and timing of therapy with antiseizure medication should be individualized, taking into account the risk of recurrence and the likelihood of side effects of the medication in a particular patient. Among people with only a single seizure, the proportion in whom serious side effects of continuous antiseizure medication will occur generally exceeds the proportion who will have an additional seizure in the ensuing five years.^{2,4,33} On the other hand, among those with two or more unprovoked seizures, the risk of additional seizures is higher than the risk of side effects of medication. Our data suggest that people with two or more unprovoked seizures should be treated.

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