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Seizure remission in adults with long-standing intractable epilepsy: An extended follow-up

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Summary Recent studies have provided much needed data on the probability of seizure remission among adults with chronic intractable epilepsy treated medically. Here we provide an extended follow-up to our earlier study in order to provide a more comprehensive picture of long-term prognosis in this patient population during medical treatment. The prevalence cohort was followed for two outcomes—complete seizure remission for ≥12 months and subsequent seizure relapse among those attaining a seizure remission. The study outcomes were estimated using Kaplan—Meier analysis. We found that the probability of attaining a ≥12 months of complete seizure freedom to be approximately 3—4% per year through 8 years of follow-up. By year 5 since the start of seizure remission, the cumulative probability of seizure relapse was 81%, although only half of the patients with seizure relapse went on to experience their previous seizure frequency.

Introduction

Until recently, there have been limited data regarding seizure prognosis in adults with medically treated intractable epilepsy. Several recent studies have provided data on the probability of attaining seizure freedom among this seriously affected group (Callaghan et al., 2007; Luciano and Shorvon, 2007; Choi et al., 2008). These longitudinal studies report that 4—5% will enter prolonged seizure free period annually. The limitation of these studies has been a relatively brief follow-up duration, ranging between 18 months and 3.9 years. In addition, only one of the studies reported annual probability of subsequent seizure relapse after attaining seizure remission. We herein report an extended follow-up of one of these studies (Choi et al.,

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2008). With longer follow-up and more patients experiencing seizure remission and relapse, this study provides a more comprehensive picture of long-term prognosis in this patient population.

Methods

Sample and procedure

We identified a retrospective cohort of 187 adults with intractable epilepsy seen in 2001 at the Columbia Comprehensive Epilepsy Center and followed through October 2009. To be considered intractable, study subjects had to meet the following criteria:

1. Continuing seizures despite ≥2 adequate trials of antiepileptic medications (AEDs) as determined by the treating physician at the center,
2. Average seizure frequency of ≥1 seizure per month for at least 3 consecutive months prior to index date,
3. ≥18 years old.

The index date was the date of a first visit in 2001 in which they met inclusion criteria. Excluded were those with a diagnosis of non-epileptic psychogenic seizures.

Study endpoints

Dependent variables

Briefly, the primary outcome of the study was achieving a ≥12 month seizure remission. Remission was defined as being free of any seizures by self-report. The secondary outcome was the occurrence of an additional seizure after experiencing a ≥12 month seizure remission.

When the exact start date of seizure remission or seizure relapse was not noted in the chart, the date of first clinic visit in which these outcomes were reported was considered the date of the outcome.

Independent variables

Clinical variables tested for association with study endpoints included:

1. History of prior epilepsy surgery.
2. Status epilepticus.
3. Age of onset.
4. Epilepsy syndrome classification.
5. Mental retardation.
6. Febrile seizure.
7. Etiology.
8. Mesial temporal lobe sclerosis.
9. Duration of epilepsy.

Criteria for epilepsy syndrome classification, for mental retardation, and etiology have been previously described (Choi et al., 2008).

Statistical analysis

Kaplan–Meier estimates analysis

Seizure remission: Kaplan–Meier analysis was used to estimate the cumulative probability of ≥12 month seizure remission during medical treatment (Kaplan and Meier, 1958). Time to event was defined as the duration between index date and 365 days after the start date of seizure remission. Observations were censored (1) on the date of last clinic visit if subjects did not have primary study outcome by their last clinical visit, (2) on the date of epilepsy surgery if performed (37 individuals had epilepsy surgery after their index date), or (3) on the date of death.

Seizure relapse: Kaplan–Meier analysis was used to estimate the cumulative probability of seizure relapse among those who had attained ≥12 month seizure remission. Time to event was defined as the duration between the beginning of ≥12 month seizure remission and the date of seizure relapse. Observations were censored on the date of last clinical visit if subjects did not have seizure relapse by their last clinic visit.

Table 1 Demographics of cohort.

Characteristics	
Female gender—*n* (% of total)	99 (53%)
Age[a]—mean (SD) at study entry	41 years (±12.4)
Follow-up time in years—mean (SD)	5.9 (±2.4)
Duration of epilepsy[a]—mean (SD)	25.6 years (±14.7)
Epilepsy classification—*n* (% of total)	
Idiopathic generalized (IGE)	8 (4%)
Localization-related (LRE)	156 (83%)
Symptomatic generalized (SGE)	20 (11%)
Other	3 (2%)
Number of failed AEDs[a]—mean (SD)	6 (±3)

Other epilepsy syndrome: 1 subject with both LRE and SGE, 1 subject with both LRE and IGE, and 1 subject with an unclassifiable epilepsy type.

[a] Mean age at the time of enrollment in study.

Cox proportional hazards analysis

We fitted Cox proportional hazards (Cox, 1972) models to the data to estimate the association (1) between clinical factors and ≥12 month seizure remission, and (2) between clinical factors and seizure relapse following remission. Each predictor variable was analyzed independently. Hazard ratios (HR) and 95% confidence interval values were determined.

All analyses were conducted with Stata statistical software (College Station, TX). This study was approved by the Institutional Review Board at the Columbia University Medical Center.

Results

The mean follow-up was 5.9 years (SD ± 2.4 years) with a total of 1108 person years (Table 1). The median follow-up was 7.0 years. During the study, 12 (5.3%) subjects died, 37 (19.8%) subjects were referred for and had epilepsy surgery, and 46 (24.6%) subjects were lost to follow up during the study.

Kaplan–Meier estimate

Out of 187 subjects, 25 (13%) attained a seizure remission of ≥12 months during medical management. Fig. 1 shows the number of subjects that met our study endpoints by the epilepsy syndrome classification. As seen in Fig. 2, the estimated annual probability of achieving a ≥12 month seizure remission was roughly 4%. To determine whether each ≥12 month seizure remission was due to changes in AEDs, we examined the three-month period preceding the start date of seizure remission. Nineteen (76%) of 25 subjects had seizure remission occurring in conjunction with change in

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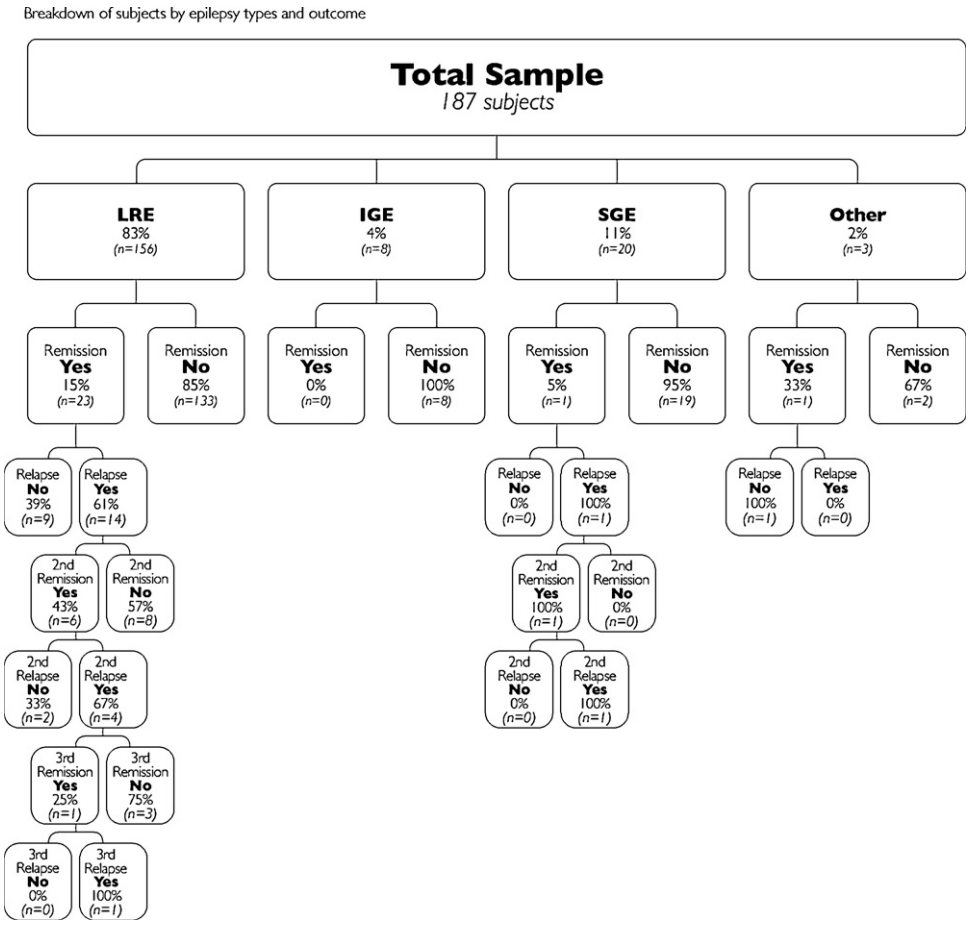

Figure 1 Breakdown of 187 patients with intractable epilepsy by epilepsy types and outcome.

medication, while 6 (24%) of 25 subjects had no changes to their medication in the three-month period prior to the start of remission.

Among 25 individuals entering remission during medical management, 15 (60%) subsequently relapsed. The mean duration of remission in 15 subjects who relapsed was 2.4 years (SD ± 1.2). The mean duration of remission among the 10 subjects who were still in remission at the end of follow-up was 3.4 years (SD ± 1.8 years). As seen in Fig. 3, the estimated annual probability of seizure relapse was approximately 25%. Of the 15 who relapsed after attaining a ≥12 months of seizure remission, 7 (47%) subsequently achieved

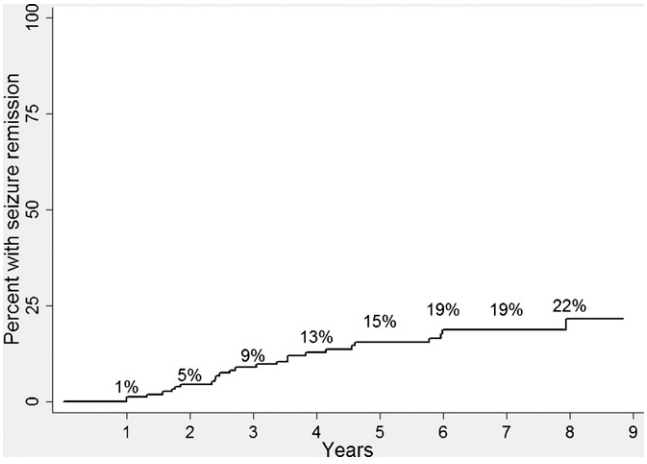

Figure 2 Kaplan–Meier estimate of cumulative probability of achieving a ≥12-months seizure remission in 187 adults with intractable epilepsy treated medically.

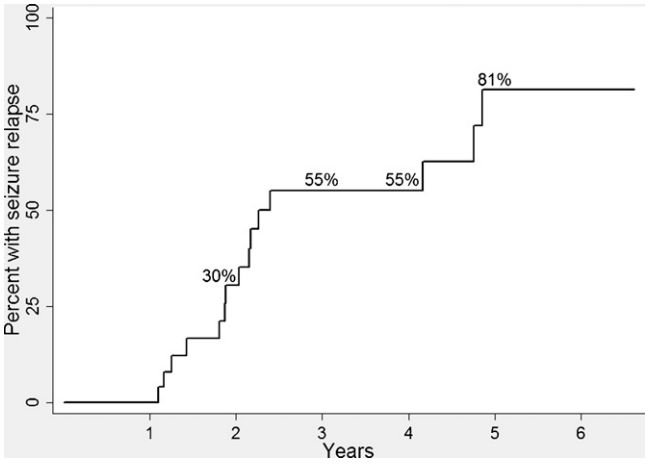

Figure 3 Kaplan–Meier estimate of cumulative probability for subsequent seizure relapse (in the 25 subjects who achieved a ≥12-months seizure remission).

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Table 2 Association between clinical characteristics and achieving ≥12 months of seizure remission.

Predictor variables	(*N* = 187)	
	HR	95% CI
History of previous epilepsysurgery (*n* = 12)	2.22	(0.76, 6.47)
Status epilepticus[a] (*n* = 16)		—
Age of onset[b]	1.05	(0.65, 1.70)
Mental retardation (*n* = 36)	0.52	(0.18, 1.52)
Febrile seizure (*n* = 20)	1.6	(0.60, 4.25)
Known etiology (*n* = 80)	0.76	(0.33, 1.75)
MTS (*n* = 20)	1.13	(0.27, 4.79)
Duration of epilepsy >10 year (*n* = 152)	0.56	(0.22, 1.40)
Number of failed AED >5 (*n* = 90)	0.83	(0.38, 1.83)

[a] No one with remission had status epilepticus.
[b] Age of onset analyzed using categories: ages 0—9, 10—20, and >20.

Table 3 Association between clinical characteristics and experiencing subsequent seizure relapse (in the 25 subjects that achieved ≥12 months of seizure remission).

Predictor variables	(*N* = 25)	
	HR	95% CI
History of previous surgery (*n* = 4)	0.80	(0.17, 3.68)
Status epilepticus (*n* = 0)[a]	—	
Age of onset[b]	0.99	(0.43, 2.28)
Mental retardation (*n* = 4)	2.08	(0.56, 7.80)
Febrile seizure (*n* = 5)	1.68	(0.44, 6.44)
Known etiology (*n* = 9)	0.79	(0.26, 2.47)
MTS (*n* = 2)	1.94	(0.42, 8.88)
Duration of epilepsy >10 year (*n* = 19)	0.78	(0.24, 2.51)
Number of failed AED >5 (*n* = 12)	1.43	(0.50, 4.12)

[a] HR could not be calculated because no one had prior history of status epilepticus.
[b] Age of onset analyzed using categories: ages 0—9, 10—20, and >20.

a second ≥12 month seizure remission of which 5 (71%) had a secondary relapse. Among the 15 subjects with relapse: 8 (53%) had seizure relapse in association with changes in their AED (5 subjects lowered or skipped their medication, and 3 subjects had medication reduction recommended by their doctor); 1 (7%) relapsed in the setting of binge drinking; 1 (7%) relapsed in the setting of sleep deprivation; 5 (33%) had no factors associated with seizure relapse. Two subjects did not have further follow-up after their seizure relapse. We examined subsequent seizure frequency in the 13 subjects after their relapse: 6 (46%) went on to meet our definition of refractory (seizure frequency of monthly seizure on average); 6 (46%) had infrequent seizures (<1 seizure a year) or achieved further seizure remission; and 1 (8%) died within a month of seizure relapse.

Cox proportional hazard ratios

The associations between clinical factors with seizure remission and between clinical factors with seizure relapse were also examined. None of the variables reached statistical significance (Tables 2 and 3).

Outcome in 37 patients who had epilepsy surgery

Of note, there were 37 subjects who had epilepsy surgery after starting this study. Their data during medical treatment were censored on the date of their surgery. Postsurgical outcome in these patients are as follows: 17 subjects (46%) had ≥12 months seizure remission. Of the 17 postsurgical patients who achieved seizure remission, 6 subjects subsequently experienced seizure relapse. The mean duration of seizure remission in these 17 subjects was 3.57 years (SD ± 1.6 years).

Discussion

Based on our definition of intractability, our prevalence cohort was comprised of 187 adults, identified from a pool of 1308 patients seen at our tertiary-care epilepsy center in 2001 and followed for their outcome status through 2009. In this current study, we found a continuing probability of ≥12 months seizure freedom to be 4% per year through 8 years of follow-up during medical treatment, which is consistent with what we previously found in our earlier study.

Until recently, long-term seizure prognosis data have mostly been available for the pediatric population, making counseling adult epilepsy patients with intractable epilepsy about their prognosis difficult. The pediatric studies showed seizure remission occurring in about 20% of pediatrics patients (Berg et al., 2006), or an annual seizure remission probability of about 4% per year (Huttenlocher and Hapke, 1990). Within the last several years, three studies of prognosis in adults with intractable epilepsy have demonstrated similar findings, with (1) an annual seizure remission probability of 4—5% per year (Callaghan et al., 2007; Choi et al., 2008), and (2) approximately a third of 155 patients becoming seizure free during a mean follow-up of 18 months (Luciano and Shorvon, 2007). With the mean follow-up duration of these three adult patient studies ranging between 18 months and 3.9 years, the probability for subsequent seizure relapse was not uniformly reported. With our prevalence cohort from 2001 through 2009, this study confirms our prior estimate of seizure remission and provides a more complete picture of whether seizure remissions in adults with intractable epilepsy are transient or permanent.

Among those who attained remission in our study, 60% (15 of 25) ultimately relapsed, although a few of these patients had multiple remission/relapses (Fig. 1). Factoring in duration of follow-up, the cumulative probability of seizure relapse was high at 81% by the fifth year from the start of seizure remission. As previously reported (Berg et al., 2009), we also found a small number of patients who experienced multiple remissions and relapses (7 patients experienced two episodes of seizure remissions, with one of them experiencing a third episode of seizure remission). Although most of seizure remissions occurred in association with medication changes, 24% of seizure remission was not associated with any changes in medications. Similarly,

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although many relapses occurred in the setting of changes in medications (i.e., skipping or reducing medications), 33% of seizure relapse was associated with no clear precipitating factors.

Although we did not identify any statistically significant clinical variables that predicted seizure remission or seizure relapse, we found the same directionality and magnitude of risks similar to those found in two other recent studies (Callaghan et al., 2007; Luciano and Shorvon, 2007). For example, we found that the presence of mental retardation, long duration of epilepsy (>10 years), and increased number of failure drug therapies (>5) were less likely to be associated with seizure remission during medical management (Table 2). On the other hand, presence of mental retardation, history of febrile convulsion, MTS, long duration of epilepsy (>10 years), and increased number of failed drug therapies (>5) were more likely to lead to seizure relapse during medical management (Table 3), if seizure remission happened to occur. Our strict definition of intractable epilepsy for inclusion in this study restricted the sample size, which limited the power to detect small to moderate associations. The recently formulated definition of intractable epilepsy by the International League Against Epilepsy (Kwan et al., 2009) — failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules to achieve sustained seizure freedom — is less restrictive and may have important implications for future studies examining the natural course and outcomes among patients with intractable epilepsy.

Our study has clear limitations. First, we were unable to identify the age of onset of intractability or the duration of intractability as a predictor variable for seizure remission or relapse. Given our retrospective chart review design, detailed seizure frequency early in the course of epilepsy was not generally available in the charts, thus we were not able to assess when patients would have met our definition of intractability. Second, we were not able to determine whether patients had any previous periods of remission, so we were not able to test whether antecedent remission and relapse was predictive of subsequent remission and relapse, as previously found in a study following children prospectively from initial diagnosis of epilepsy (Berg et al., 2006). Third, current outcome was unknown for 46 subjects who were lost to follow up at some time during our 8 year-period study. The Kaplan—Meier analysis does allow these subjects to contribute information until they became censored from our analysis.

Although seizure remission occurs in about 4% of adults with intractable epilepsy per year, a sizable proportion goes on to eventually relapse. However, we found that among those who relapsed after their remission, only about half of them went on to experience their previous seizure frequency.

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