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FULL-LENGTH ORIGINAL RESEARCH

Remission and relapse in a drug-resistant epilepsy population followed prospectively

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Summary

Purpose: We investigated the cumulative probability of seizure remission and relapse in an adult population with drug-resistant epilepsy and frequent seizures. In addition, we determined clinical predictors of remission and relapse in this population.

Methods: In 2003, we identified 246 patients at a single center with drug-resistant epilepsy defined as at least one seizure per month and failure of at least two antiepileptic drugs. These patients were followed prospectively (cohort design). We examined the cumulative probability of seizure remission and relapse in this population using Kaplan-Meier methodology. Clinical predictors of remission and relapse were also evaluated using Cox regression analysis.

Key Findings: The estimated cumulative probability of 12-month seizure remission was 34.6% at 7 years in the entire population and 33.4% when limited to those without surgery. The risk for relapse after a 12-month period of seizure remission was 71.2% at 5 years. Negative predictors of seizure remission included developmental delay, symptomatic generalized epilepsy syndrome, duration of intractability, and number of antiepileptic drugs failed. Localization-related epilepsy was the only negative predictor of relapse.

Significance: Among patients with drug-resistant epilepsy, 5% per year enter seizure remission even with a follow-up of 6 years. However, a substantial proportion of these patients relapse after the first year following a remission. The large proportion of patients entering a significant remission gives these patients hope; however, caution should be advised when discussing the likelihood of future seizures.

KEY WORDS: Epilepsy, Refractory, Relapse.

Epilepsy is a common neurologic disorder with a prevalence of 0.4–1% (Duncan et al., 2006). Previous studies have estimated that between 20% and 40% of patients have drug-resistant epilepsy (DRE) (Annegers et al., 1979, Elwes et al., 1984; Shafer et al., 1988; Anonymous, 1992; Cockerell et al., 1995; Sillanpaa et al., 1998; Kwan & Brodie, 2000; Lindsten et al., 2001). Patients in this group are affected in multiple ways, including decreased educational attainment, employment, and marriage (Sperling, 2004). Furthermore, they are at increased risk for mortality and psychiatric comorbidities, and are unable to drive (Sperling, 2004). Clearly, DRE has a major impact on the lives of these patients.

Until recently, there had been only a few studies focusing on DRE, including those of Huttenlocker, Silanpaa, and Berg, all focusing on children (Huttenlocher & Hapke, 1990; Sillanpaa, 1993; Berg et al., 1996; Sillanpaa et al., 1998; Berg et al., 2006, 2009). Silanpaa et al. investigated predictors of long-term remission in children and found that rapid response to therapy and idiopathic epilepsy were associated with remission (Sillanpaa et al., 1998). Berg et al. performed a case–control study that identified remote symptomatic epilepsy, younger age at onset, and status epilepticus as predictors of intractability (Berg et al., 1996). In a separate analysis, Berg et al. found that idiopathic epilepsy and lower seizure frequency were predictive of a remission after failure of two antiepileptic drugs (AEDs) (Berg et al., 2009). Although long-term predictors of epilepsy have been studied in pediatric populations for years, study of adult populations has lagged behind.

More recently there have been a few adult studies investigating the course of DRE. In 2007 Luciano et al. followed a retrospective cohort of 155 patients who were seizing at least once per month and had a history of epilepsy of at least 5 years (Luciano & Shorvon, 2007). After a median of 19 months, 28% of these patients became seizure free for at

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least 12 months following the addition of an AED. Predictors of seizure remission included less than five previous AEDs, idiopathic epilepsy, and a duration of epilepsy of less than 10 years. In 2007, our group reported on 246 patients with DRE defined as a seizure frequency exceeding one per month and failure of more than two AEDs (Callaghan et al., 2007). We found that 5% per year had a 6 month or greater seizure-free period over 3 years of observation. Negative predictors of seizure remission included number of AEDs failed, younger age of intractability, developmental delay, and a history of status epilepticus. In 2008, Choi et al. described 187 patients using the same definition of DRE as used by our group, (Callaghan et al., 2007) and reported 4% per year achieving 1 year or greater seizure remission (Choi et al., 2008). All of these studies showed a higher than expected cumulative probability for seizure remission in DRE compared with Kwan and Brodie's report (2000), which showed that only 11% of patients that failed the first AED secondary to lack of efficacy become seizure free (Kwan & Brodie, 2000). Despite the lack of consensus on the definition of DRE, similar factors emerged as clinical predictors of remission in these later studies.

The studies described raise as many questions as they answer. Seizure ''remission'' was usually defined as one or more years of seizure freedom, with the patient remaining seizure free at the time of the last visit. Although this can be a meaningful length of time in the course of epilepsy, it does not necessarily translate to the ultimate goal of epilepsy therapy, which is a long-term or even permanent seizure freedom. In addition, prior studies did not address whether these patients went on to have sustained seizure remissions. Only Choi et al. (Choi et al., 2008) commented on relapse rate, but the duration of follow-up was short. Furthermore, studies to date did not identify risk factors for relapse in patients with DRE who enter a seizure remission, and the three studies following adult cohorts with DRE have had only 18 months to 4 years of follow-up to date. Therefore, the purpose of this study is to investigate the cumulative probability for remission and relapse in a DRE population followed prospectively over a longer time period. Because DRE causes significant morbidity and mortality, there are important unanswered questions to address, regarding when to try additional medications, advocate surgery or vagal nerve stimulators, and when to advise patients that driving is safe. Insight into the natural history of DRE is the first step toward providing these answers.

Methods

In 2003, we identified a retrospective cohort of 246 patients who met the following definition of DRE: (1) Greater than or equal to one seizure per month for the 3 months prior to the index date and (2) failed greater than or equal to two AEDs prior to the index date (Callaghan et al., 2007). All patients had been seen in 2000 (index date) at the University of Pennsylvania Epilepsy Center and had at least one follow-up visit. Since that time we have followed this group prospectively through 2006. We initially documented demographics as well as seizure type, epilepsy syndrome, etiology of epilepsy, presence of developmental delay (IQ <70), any history of status epilepticus (seizures lasting greater than 30 min), age of onset, age of intractability, previous number of AEDs failed, electroencephalography (EEG) and magnetic resonance imaging (MRI) results, seizure frequency at index, and number of years at the epilepsy center. During the subsequent follow-up, we have documented all changes in AEDs including dose changes and reason for failure, and all seizure remissions >12 months including seizure remission at the time of the last visit. Relapse was defined as recurrence of any seizure including simple partial seizures (auras) after becoming seizure free for greater than 1 or 2 years. Interventions were recorded such as vagal nerve stimulators, surgery including temporal lobectomy, intracranial monitoring, and deep brain stimulation. The number of AEDs tried since the index date, as well as the date and status at last follow-up were obtained. Follow-up methods included chart review, and, for those not seen within the past year, search of the National Social Security death index prior to additional attempts at direct contact using last known phone number.

Statistical analysis

Kaplan-Meier analyses were used to estimate the cumulative probability for a 12 month and 24 month or greater seizure remission in adults with DRE. Patients were censored if they died or were lost to follow-up. These analyses were repeated separating the cohort into those with and without surgery. Surgery was defined as any therapeutic intracranial surgical intervention, with most being temporal lobectomies. Among those with surgery, the follow-up period began at the time of surgery, whereas for those without surgery, follow-up began at the index date in 2000. We used Cox proportional hazards regression to examine predictors of entering a seizure remission in all patients with DRE. Factors examined included developmental delay, history of status epilepticus, epilepsy syndrome, age at onset, duration of intractability, and number of AEDs failed. Univariate analyses were conducted and those factors that were statistically significantly associated with entering a seizure remission were simultaneously entered into an adjusted model.

Among those patients who achieved a 12 or 24 month or greater seizure remission, Kaplan-Meier analyses were used to estimate the cumulative risk for seizure relapse. Patients were censored if they died or were lost to follow-up. For these patients, follow-up began at the time of their 12- or 24-month seizure remission. We examined predictors of seizure relapse after a seizure remission using Cox proportional hazards regression. Factors examined as predictors were the same as those used in the analysis of predictors of seizure remission.

Results

In our DRE population, 177 (80.5%) had localization-related epilepsy, 27 (11%) had symptomatic generalized epilepsy, 17 (6.9%) had primary generalized epilepsy, and 4 (1.6%) had another epilepsy syndrome (Fig. 1). The mean and median age of this patient population at the index date was 40 years, with a range of 12–83 years. Fifty-nine percent of the population was female. The median duration of epilepsy was 25 years [interquartile range (IQR) 14–36 years], and the median duration of intractability was 18.6 years (IQR 6.8–31.9 years). The median duration of follow up was 5.9 years (IQR 5.1–7.2 years). The reasons for drug failure before index date were maximum tolerated dose in 54% of cases, idiosyncratic reaction in 6.5%, intolerable side effect in 19%, and unknown reasons in 21%. Twenty-four of the patients were deceased at last follow-up. In addition, 20 patients (8%) were lost to follow-up despite attempts to contact patients at their last known phone number.

Outcomes

Remission

Fifty-nine of 246 patients (24.0%) obtained a 12-month seizure remission. Forty-one patients became seizure free with medication change, 10 after surgery, and 8 with no surgery or medication change.

The cumulative probabilities of greater than 12-month seizure freedom among the entire cohort with DRE, restricted to those without any brain surgery, and those with surgery are listed in Table 1 (Figs. 2 and 3). The cumulative probabilities of greater than 24-month seizure freedom among the entire cohort is also listed in Table 1 (Fig. 1).

Clinical predictors of seizure remission

Several factors were associated with a decreased cumulative probability for a 12 month or greater seizure remission in unadjusted analysis (Table 2). These included presence of developmental delay, symptomatic generalized epilepsy syndrome, longer duration of intractability, and

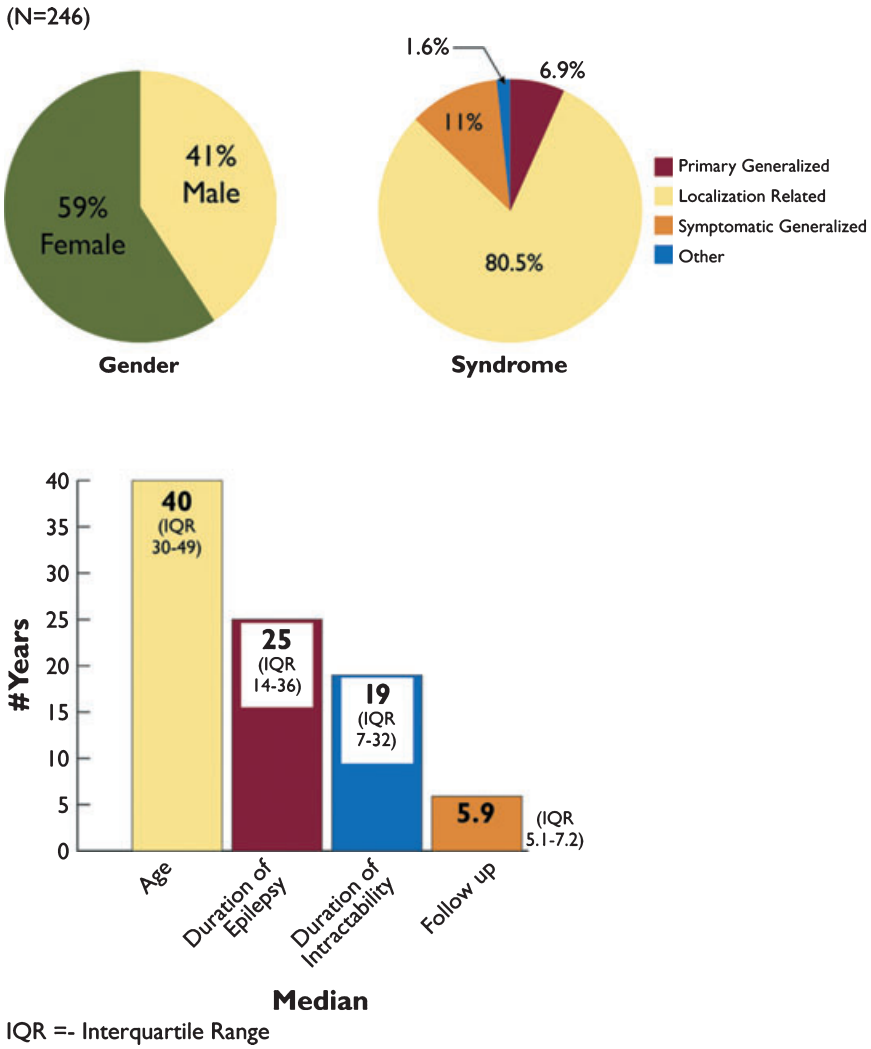

Figure 1.
Patient Demographics and Clinical Characteristics. Demographics and clinical characteristics of the adult drug-resistant epilepsy cohort (N = 246).
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Table 1. Cumulative probabilities remission among the entire cohort (12 and 24 months), restricted to those without any brain surgery, and including only those with surgery

End point	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
12 Month remission	7.0% (4.4–11.2)	12.1% (8.5–17.1)	17.9% (13.4–23.7)	21.9% (16.9–28.1)	27.5% (21.5–34.7)	34.6% (26.4–44.4)
12 Month remission, no surgery	6.3% (3.7–10.6)	11.5% (7.8–16.7)	16.9% (12.3–22.9)	20.3% (15.2–26.7)	25.2% (19.3–32.5)	33.4% (24.7–44.2)
First remission, surgery	44.7% (27.6–66.4)	44.7% (27.6–66.4)	49.3% (31.5–70.6)	–	–	–
24 Month remission	0.00%	5.3% (3.0–9.3)	8.9% (5.7–13.8)	11.70% (7.9–17.1)	13.90% (9.6–19.8)	22.70% (14.9–33.8)

95% Confidence intervals in parentheses.

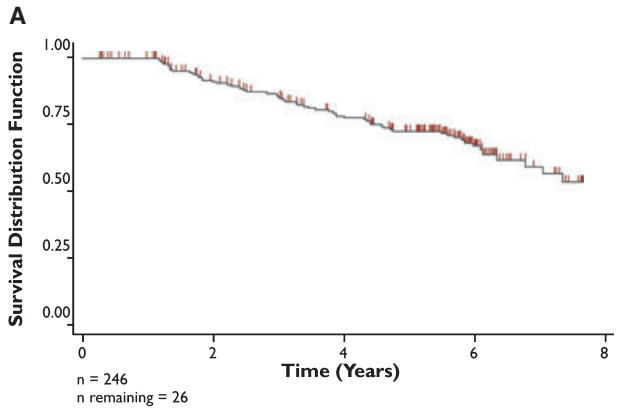

Figure 2.
Time to first seizure remission. Kaplan-Meier curves of time to 1-year seizure remission (**A**) and time to 2-year seizure remission (**B**).
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number of AEDs failed. Neither age at onset nor status epilepticus was statistically significantly associated with seizure remission. In adjusted analysis, only the number of AEDs failed was an independent negative predictor of seizure remission (Table 2).

Relapse

Thirty-four of the 59 patients who obtained a 12-month remission had a subsequent relapse. The cumulative risk of subsequent seizures after a 12-month seizure remission was 40.1% [95% confidence interval (95% CI) 28.4–54.4%], 55.7% (95% CI 42.0–70.4%), 58.5% (95% CI 73.0–44.5%), 65.4% (95% CI 50.6–79.7%), and 71.2% (95% CI 54.7–85.8%) at 1–5 years, respectively (Fig. 3). The cumulative risk of relapse after a 24-month seizure remission was 23.6% at year 1 (95% CI 11.3–45.4%), 28.1% at year 2 (95% CI 14.4–50.4%), and 46.7% at year 3 (95% CI 27.5–70.7%) (Fig. 4). All patients that relapsed had seizures other than just simple partial seizures (auras). Of the 34 patients who relapsed, 18 (53%) had a second remission of greater than 12 months. For 8 of these 18 patients, the second remission lasted to the end of follow-up. Seven of the 18 patients had a second relapse, and 3 had at least three total relapses.

Clinical predictors of relapse

Relapse was less likely for localization-related epilepsy (Table 2). Several factors examined that were not statistically significantly associated with relapse, included developmental delay, a history of status epilepticus, age at onset, duration of intractability, and number of AEDs failed.

Effect of medication change on relapse

Of the 59 patients that entered remission, 50.8% had no subsequent change in their AED regimen, 18.6% had a decreased dose, and 13.6% had discontinuation of an AED. In the group that relapsed 55.9% had no change in medication, 26.5% had a decreased dose, and 5.9% had an AED discontinued. Similarly, in the group with sustained remissions without relapse, 44.0% had no medication change, 8.0% had a decreased dose, and 24.0% had an AED discontinued. Among the patients who relapsed, 44.1% had a mild course (1–2 total seizures), 17.6% moderate (<1 seizure per month), and 26.5% severe (>1 seizure per month). Taken together, 61.7% of those that relapsed had a lower seizure frequency than they experienced at study entry.

Discussion

An unexpectedly high proportion of adults meeting our definition of DRE attained a seizure remission of 12 months or more (~5%/year). This is the same proportion we had previously shown with only 3 years of follow-up, indicating

Table 2. (A) Risk factors for 1 year or greater remission, (B) Risk factors for relapse after 1 year or greater remission

Variable	n (% remission)	RR (95% CI)	Adjusted RR (95% CI)
(A)			
Developmental delay			
Yes	69 (14.5)	0.45 (0.23–0.90)	0.60 (0.29–1.2)
No	177 (27.7)	1.0 (Referent)	1.0 (Referent)
Status epilepticus			NA
Yes	39 (12.8)	0.46 (0.18–1.2)	
No	207 (26.1)	1.0 (Referent)	
Epilepsy syndrome			NA
Localization-related	198 (25.8)	0.98 (0.14–7.1)	
Symptomatic generalized	27 (3.7)	0.118 (0.007–1.9)	
Primary generalized	17 (35.3)	1.4 (0.16–11.4)	
Other	4 (25.0)	1.0 (Referent)	
Age at onset			NA
<15 years	151 (25.8)	1.2 (0.70–2.1)	
≤15 years	95 (21.1)	1.0 (Referent)	
Duration of intractability			
≥10 years	171 (19.9)	0.52 (0.31–0.88)	0.76 (0.43–1.3)
<10 years	75 (33.3)	1.0 (Referent)	1.0 (Referent)
Number of AEDs failed			
≥6	145 (15.9)	0.39 (0.23–0.66)	0.46 (0.27–0.80)
<6	101 (35.6)	1.0 (Referent)	1.0 (Referent)
Variable		**n (% relapse)**	**RR (95% CI)**
(B)			
Developmental delay			
Yes		10 (50.0)	0.85 (0.33–2.2)
No		49 (55.1)	1.0 (Referent)
Status epilepticus			
Yes		5 (80.0)	1.57 (0.55–4.5)
No		54 (51.9)	1.0 (Referent)
Epilepsy syndrome			
Localization-related		51 (51.0)	0.31 (0.04–2.3)
Symptomatic generalized		1 (100.0)	1.0 (0.11–9.0)
Primary generalized		6 (66.7)	0.74 (0.05–11.9)
Other		1 (100.0)	1.0 (Referent)
Age at onset			
<15 years		39 (66.1)	0.77 (0.38–1.6)
≥15 years		20 (60.0)	1.0 (Referent)
Duration of Intractability			
≥10 years		34 (58.8)	1.2 (0.57–2.4)
<10 years		25 (48.0)	1.0 (Referent)
Number of AEDs failed			
≥6		23 (69.6)	1.8 (0.90–3.6)
<6		36 (44.4)	1.0 (Referent)

RR, relative risk.

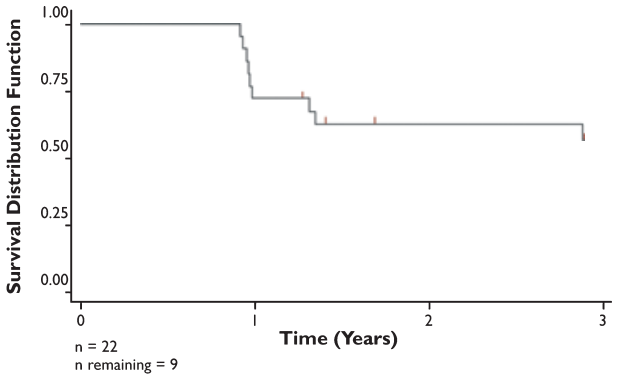

Figure 3.
Time to first seizure remission in the surgery group. Kaplan-Meier curve of time to 1-year seizure remission in the surgery group (any intracranial surgical intervention, with most being temporal lobectomies) starting from the surgery date.
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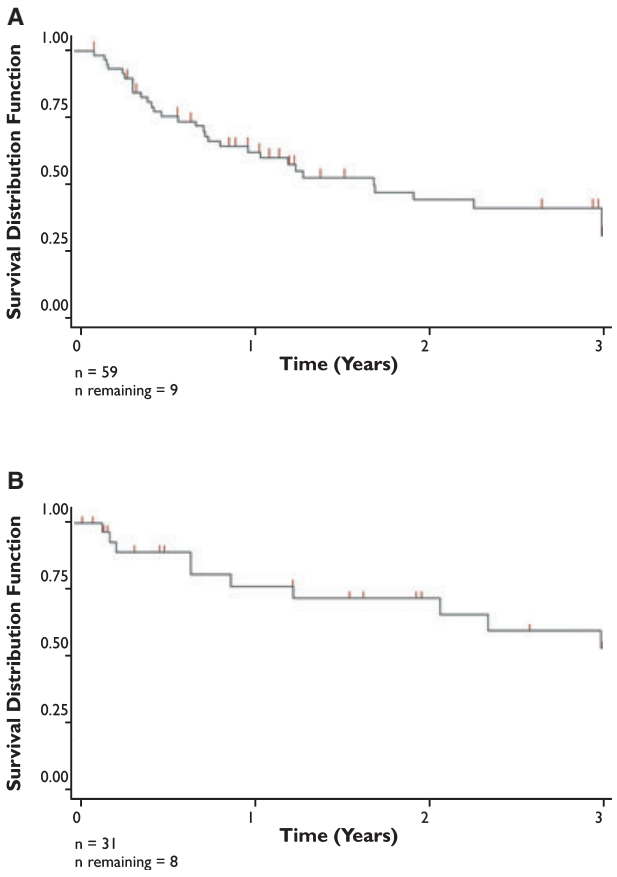

Figure 4.
Time to relapse after a significant seizure remission. Kaplan-Meier curves of time to relapse after 1-year seizure remission (**A**) and after 2-year seizure remission (**B**).
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that this proportion remains stable over a 6-year period (Callaghan et al., 2007). Therefore, about one third of patients with DRE can be expected to experience a prolonged seizure remission over a 6-year period, a percentage that is likely to grow over time. Given the fact that this population was initially seizing at least once per month, a

12-month seizure remission is a meaningful change. It is important for patients with DRE to be aware that there is a substantial chance of a prolonged seizure remission even though permanent seizure freedom is much less likely. The short-term prognosis for patients with frequent seizures is perhaps not as bleak as previously believed.

However, a large percentage of patients that achieve a 12-month or greater seizure remission eventually relapse (~71% at 6 years after onset of the remission). This is also true after a 24 month or greater seizure remission (~47% at 4 years after onset of the remission). As a result, epileptologists must use caution when discussing seizure prognosis in this patient population, a particularly important consideration when addressing the question of when patients should return to driving. Currently, in most states, patients are restricted from driving for 6–12 months following a seizure. However, at least in this drug-refractory population, many relapses occur well after a 1-year seizure free period. In fact, the relapse curve does not start to level off until approximately 2 to 3 years after the patient's last seizure. It is possible that a longer time without driving is necessary for the previously treatment-resistant patient to avoid potentially devastating consequences. The relapse rate also raises the question of when a patient with DRE should be considered cured, as our findings suggest that even multiple years after a last seizure there is still a significant risk of recurrence. Although we were unable to systematically address AED discontinuation, it would appear prudent to continue therapy in patients who have had a 1-year seizure remission, since more than half of them have not had their last lifetime seizure.

Interestingly, the high probability of relapse found in this study was also seen by Berg et al. (Berg et al., 2009). They followed an incident cohort of 128 children with drug-refractory epilepsy defined as failure of two AEDs due to lack of efficacy and no remission greater than 1 year by the time of the second AED failure. In their population, 68% of their patients experienced a relapse after a 12-month remission after a median follow-up of 10 years in comparison to the 58% seen in our study after 6 years. However, they reported a probability of a 1-year remission at 5 years of 47% compared to 22% in our prevalence cohort. The contrasting probability of remission is likely due to several differences in these two studies, including the different age distributions (children versus adults), type of cohorts (incident versus prevalence), and definition of drug-resistant epilepsy (>1 seizure per year versus >1 seizure per month). Similarly, Schiller et al. described a cohort of 256 patients who had a greater than 1 year remission and reported a substantial degree of relapse when followed for 5 years (40.2%) (Schiller, 2009). The major difference between this cohort and ours is that we included only those with refractory epilepsy at baseline having one seizure per month, whereas Schiller et al. included all patients with epilepsy. Despite these substantial differences, all of these studies agree that a substantial number of patients with drug-refractory epilepsy experience significant remissions, but that a large proportion of these patients also relapse.

The present study found four factors associated with a decreased risk for a 12-month or greater seizure remission, but no factors were associated with subsequent relapse. The four factors associated with remission were developmental delay, symptomatic generalized epilepsy, duration of intractability, and number of AEDs failed. However, only number of AEDs failed remained a statistically significant predictor in the adjusted model. This result is not surprising given the work of Schiller and Najjar, who discovered that remission is a function of the number of past AEDs failed in a cohort of all patients with epilepsy undergoing new AED therapy (Schiller & Najjar, 2008). Our data indicate that this is also a predictor of remission in a drug-resistant cohort. These results are in agreement with our previous study in the same cohort where follow-up was shorter and a more brief seizure-free period defined remission, with the exception that the prior study showed that a history of status epilepticus was associated with a reduced likelihood of remission (Callaghan et al., 2007). In the current analysis, there was a trend for a history of status to be associated with a reduced likelihood of remission (rate ratio 0.46), which was also seen as a predictor of intractability by Berg et al. (Berg et al., 1996). Our study suggests that prior studies are not actually identifying predictors of long-term treatment success, since those in the ''seizure free'' group at the end of the observation period included many who had been seizure free for <3 years, and a substantial number of those would be expected to relapse in future years. The lack of predictors associated with relapse was surprising given that we expected that some of the same factors that were associated with remission would also impact relapse. However, the relatively small numbers in the relapse group may have limited our ability to detect these associations.

The reasons for relapse in this population do not appear to be limited to medication withdrawal or dose reductions. Approximately the same number of patients with sustained remissions (32%) had medication changes as those who subsequently relapsed (32%). Therefore, there are likely factors, other than medication changes, that result in relapse after a significant remission. Among patients who relapsed, the majority (62%) had a lower seizure frequency than they experienced at study entry. This emphasizes that an important percentage of patients in this refractory population have a significant improvement in their seizure control even if they do not have a sustained remission.

There are limitations to our study. The sample size makes definitive conclusions about the clinical predictors of remission and relapse difficult. Many of these predictors barely met statistical significance and very few of them continued to meet criteria for significance in adjusted models. In addition, the lack of association between certain variables and remission or relapse does not mean that none exists. Further-

more, we were unable to evaluate predictors of longer term remission such as greater than 5 years given the length of follow-up. On the other hand, our adult DRE cohort continues to be the largest in the literature. Furthermore, many of these clinical predictors have been confirmed in the few other adult studies or in pediatric populations. Another limitation is that we studied many different variables, which increases the likelihood of an association by chance. Moreover, we chose a definition of DRE prior to the new International League Against Epilepsy (ILAE) definition (Kwan et al., 2010). This new definition agrees with our definition with respect to number of AEDs failed, although it adds rigor in regard to the definition of AED failure. Of greater importance, the new definition does not include a seizure frequency requirement such as the one seizure per month, as used in our study. If we had not used this requirement, the study would have needed to be even longer in duration. As a consequence of these differences in definition, the generalizability of our results to a refractory population with less frequent seizures is unclear. However, the advantage of establishing an initial one seizure per month or greater seizure frequency is that we could confirm that a 1-year seizure-free interval was a meaningful remission for every patient, whereas if such a seizure frequency was not established, this might not be the case. The new ILAE definition of treatment response requires no seizures for three times the prior interseizure interval. Therefore, the prior interseizure interval must be known to assess outcome. Another limitation is that we do not have information on drug adherence and its role in remission and relapse within this population. Moreover, we have followed a prevalence cohort, which incorporates a heterogeneous patient population with differing disease durations and characteristics. Our epilepsy syndrome classification is also broad and may include syndromes with differing outcomes and responses to drugs. Finally, we relied on patient reports of seizures, which may be an underestimate of their true seizure frequency.

Throughout this article we have chosen to define remission as ≥12 or ≥24 months without seizures. Even after such a remission, there is an extremely high relapse rate. It appears that after approximately 3 years of seizure remission, the likelihood of relapse stabilizes at a low rate. Further work will be needed to solidify the appropriate time interval necessary to declare a true remission, analogous to the cancer literature that has defined remission as a 5-year period based upon the risk for recurrence. Once further data are available in adult cohorts with DRE, multicenter studies can be used to truly identify factors associated with the likelihood of a lasting remission in this population.

In conclusion, adult patients with DRE have a cumulative probability for a 12-month seizure remission of 5% per year that continues over many years of follow-up. However, this population also has a high likelihood of relapse, even after the first year of seizure freedom. Physicians should give their DRE patients hope that considerable improvement can be obtained, but they should be cautious when giving a prognosis for the likelihood of complete seizure remission. Both the duration of remission and the likelihood of relapse have serious implications for the lives of these patients, particularly with respect to when they should be permitted to resume driving.

Authors' Contributions

Dr. Callaghan extracted the information from the patient's medical record, established the database, and was the main author of this text. Dr. Schlesinger performed the statistical analysis under the guidance of Dr. Hesdorffer. Mr. Rodemer and Dr. Pollard were involved in data extraction from the patient's medical record. Dr. Hauser provided epidemiologic expertise and contributed greatly to the writing of the manuscript. Dr. French was involved in study design, execution, and contributed greatly to writing of the manuscript.

Disclosure

Dr. Callaghan, Dr. Schlesinger, and Mr. Rodemer report no disclosures. Dr. Pollard reports that he is funded to conduct clinical trials through Medtronic, Esai, Lundbeck, Supernus, and UCB. Dr. Hesdorffer serves on a scientific advisory board for Pfizer Inc; has received funding for travel from GlaxoSmithKline and UCB; and receives research support from the CDC (DP002209 Role: PI), the NIH (NINDS NS043209 Role: PI of subcontract, NINDS NS31146 Role: PI of subcontract, NICHD HD042823 Role: Co-Investigator, and AUCD RT01 2008-01-01 Role: PI of subcontract), and from the HRSA Maternal and Child Health Bureau (MC00007 Role: Co-Investigator). Dr. Hauser reports that he has been a consultant to Pfizer, GlaxoSmithKline, Intranasal and he receives grant support from the Centers for Disease Control and Prevention (CDC). Dr. French has served as a consultant for the following companies, with the proceeds going to the Epilepsy Study Consortium: Cypress Bioscience Inc, Eisai Medical Research, GlaxoSmithKline, Icagen Inc., Ikano, Johnson and Johnson PRD, Marinus, NeuroVista Corporation, Novartis, Ono Pharma USA Inc, Ovation, Pfizer, Sepracor Inc., SK Life Science Inc, Special Products, LTD, Supernus Pharmaceuticals, Taro Pharmaceuticals, UCB, Inc, Upsher Smith, Valeant, and Vertex Pharmaceuticals. She has received grant support from Pfizer, UCB, Inc, Icagen, Ikano, SK Life Sciences, and Vertex. She serves as the Director of the Epilepsy Study Consortium, from which her institution receives a fixed salary support. Role of funding source: There was no funding for this investigation. Ethics committee approval: The Institutional Review Board at the University of Pennsylvania approved the use of human subjects in this study. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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