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Risk of recurrence after a first unprovoked seizure

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SUMMARY

The risk of recurrence after a first unprovoked seizure has been examined in numerous observational studies and two large, high-quality randomized trials. Overall, in untreated individuals, 40–50% can expect a recurrence within 2 years of the initial seizure. Treatment may reduce this risk by as much as half. Those at the greatest risk of recurrence have either an abnormal EEG or an identifiable neurological condition or symptoms consistent with one ("symptomatic"). Status epilepticus and a history of febrile seizures may be associated with an increased risk of recurrence in individuals with symptomatic seizures. The great majority of people (~90%) who are seen for a first unprovoked seizure attain a one to two year remission within 4 or 5 years of the initial event.

KEY WORDS: Seizure, Recurrence risk, Epidemiology, Epilepsy.

Gowers's description of the epileptic process, "each attack facilitates the occurrence of another by increasing the instability of the nerve elements" (Gowers, 1881) was immortalized in the phrase "seizures beget seizures." Because of this, and because of methodologically inadequate observations suggesting a near 100% risk of recurrence following a first unprovoked seizure, there was considerable concern about treatment of first seizures. More recent studies, including well-conducted prospective cohort studies and randomized clinical trials, have provided a much more accurate understanding of the overall risk of future recurrences and have identified factors that distinguish individuals with particularly high and particularly low risks of recurrence. The following review will cover several points: (a) a consideration of the overall risk of a recurrence based upon the major studies that have tackled this question, including both observational and randomized trials; (b) a review of those factors most consistently shown to influence the risk; (c) other seizure outcomes; and (d) additional considerations.

In this review, the recommendations and specifically the definitions provided by the ILAE Commission of Epidemiology and Prognosis for epileptic seizure, provoked seizure, unprovoked seizure, and epilepsy will be respected (Commission on Epidemiology and Prognosis and International League Against Epilepsy, 1993). These definitions are reviewed by Hauser and Beghi (2008); they are widely accepted and used by epidemiologists and clinical investigators in large part because they make good clinical sense and correspond to common, important clinical situations in which decisions regarding treatment must be made. Despite some assertions to the contrary, epidemiological and clinical investigators have found these recommendations to be highly meaningful and easy to implement in a consistent, reliable manner. This has had the cumulative benefit of creating considerable coherence and comparability among the studies in this area.

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RISK OF A RECURRENT SEIZURE

The risk of recurrence after a first unprovoked seizure has been the subject of numerous studies. This review, however, is not intended to be exhaustive but rather, selective. Specifically, it focuses primarily on large, well-powered studies, particularly large randomized trials but observational studies as well that have been rigorously conducted and analyzed.

It is difficult to discuss the overall risk of recurrence without first considering that the most powerful determinant of recurrence is treatment. This was not clearly evident in the earlier observational studies because almost all patients were treated (Hauser et al., 1990), none of the patients was treated (Stroink et al., 1998; van Donselaar et al., 1992), or treatment was by indication, according to perceived risk (Shinnar et al., 1996).

Two large-scale randomized trials provided definitive estimates of the risk of recurrence after an *untreated* first

unprovoked, seizure. These are the multicenter study from Italy, FIR.S.T (First Seizure Trial Group, 1993) and the European-wide Multicenter Epilepsy and Single Seizure study or MESS, which included both first seizures and newly recognized epilepsy (Marson et al., 2005). Based on 193 patients randomized to deferred treatment only in the event of a second seizure (i.e., initially untreated), the FIR.S.T study reported recurrence risks of 18%, 28%, 41%, and 51% at 3, 6, 12, and 24 months after the initial seizure. In the MESS study, 408 patients with a first unprovoked seizure were randomized to the deferred treatment group. Their risk of recurrence at 6 months, 2, 5, and 8 years after randomization was 26%, 39%, 51%, and 52%. On average, the observational studies, taken as a whole, provide an estimate of the 2-year recurrence risk in the range of 40%, depending on aspects of the study design (Berg & Shinnar, 1991).

Both of the randomized trials, especially the second, demonstrate a pattern seen in virtually all of the long-term observational studies of first seizures. Specifically, the risk of a recurrence is highest during the period immediately after the initial seizure. The rate, at which first recurrences occur, drops off with increasing time since the first seizure. Across a number of studies with prolonged follow-up periods, 80–90% of individuals who recur do so within 2 years of the initial seizure (Annegers et al., 1986; Hopkins et al., 1988; Boulloche et al., 1989; Hauser et al., 1990; Shinnar et al., 1996).

Predictors of a First Recurrence

Treatment

The impact of treatment on the risk of recurrence is clearly demonstrated in these two large trials. In the FIR.S.T. study, 397 patients of all ages were randomized to immediate treatment (N = 204) or deferred treatment only in the event of a recurrent seizure (N = 193) (First Seizure Trial Group, 1993). Compared to the deferred (untreated) group, the risk of recurrence in the immediate treatment group was substantially lower. At 3, 6, 12, and 24 months after randomization, the risk in the immediate treatment group was 7%, 8%, 17%, and 25% versus 18%, 28%, 41%, and 51% in the deferred group. The overall hazards ratio for immediate versus deferred treatment was 0.4 indicating a 60% reduction in the rate of relapse for immediate versus delayed treatment.

The MESS trial contained 812 study participants with a first seizure. The risk of recurrence in the 404 randomized to immediate treatment was 18%, 32%, 42%, and 46% at 6 months, 2, 5, and 8 years after randomization versus 26%, 39%, 51%, and 52% in the deferred treatment group. The overall hazards ratio was provided for the entire trial (first seizure and newly diagnosed epilepsy together) and was 1.4 for untreated versus treated arms. This translates into a treatment effect (reduction in the recurrence rate) of about 30%.

The difference in the impact of treatment between these trials is considerable (60% versus 30%) reduction. Reasons for these differences are not immediately apparent although the estimate from the MESS trial combined data from first seizure and newly diagnosed epilepsy patients. In addition, the hazards ratio was based on a much longer period of observation, up to 8 years. At 2 years after randomization, however, the impact of treatment was still much more modest in the MESS study compared with the FIR.S.T. Most of the differences between the two studies appears in the treatment groups and may reflect the degree of adherence with the initial policy to which patients were randomized. Thus, this may reflect, in part, the difference between efficacy, effect of a treatment used as planned, versus effectiveness, effect of a treatment as actually used. Nonetheless, the MESS study's untreated arm did have an overall lower risk compared with the FIR.S.T. study's untreated arm (about 12% difference at 2 years). Greater precision in estimating the overall recurrence risk does not appear to be possible currently.

EEG and neurological abnormality

Beyond the effect of treatment, other factors that are intrinsic to the individual can influence the risk of recurrence. There is no algorithm to predict with absolute certainty who will or will not have a recurrence and when that recurrence will occur. Although there are numerous studies that have examined predictors of recurrence, few gains have been made in the sophistication of these efforts. Consequently, little has occurred to advance our knowledge in this field, and what can be summarized today is very much the same as reported in reviews of this same topic written over 10 years ago (Berg & Shinnar, 1991) and reported in subsequent observational studies since then (e.g., Ramos Lizana et al., 2000; Kho et al., 2006). That said, there are two factors that are consistently associated with an increased risk of recurrence in both children and adults. These are an abnormal EEG (particularly if the abnormality is epileptiform) and a symptomatic cause or abnormal neurological exam. The two factors may have a somewhat additive effect in that patients with both a symptomatic cause and an abnormal EEG appear to have an even higher risk than those with only one of those factors (Kim et al., 2006).

In the MESS study, individuals who had normal EEGs and a normal neurological status, the lowest risk group, had a risk of a recurrence that was approximately 20%, 25%, and 30% at 1, 2, and 4 years after randomization (Kim et al., 2006). These estimates come from the trial's untreated arm and are probably the best single source of data on this matter. In a proportional hazards model, the hazards ratio for neurological disorder (essentially symptomatic cause) was 1.35 (95% CI 1.07–1.72, p = 0.013)

and for abnormal EEG was 1.54 (95% CI 1.27–1.86, $p < 0.0001$).

Interestingly, the FIR.S.T study did not find either of these factors to be associated with the risk of recurrence (First Seizure Trial Group, 1993). Most observational studies, however, do find that symptomatic etiology and the EEG are good predictors of recurrence (Berg & Shinnar, 1991; Stroink et al., 1998; Ramos Lizana et al., 2000; Kho et al., 2006).

Numerous other factors have been considered in various studies. The consistency of the findings for each when viewed across studies is imperfect.

Table 1. Distribution of presenting seizure types in patients with newly diagnosed seizures and the proportion of patients for each seizure type who presented with their first ever unprovoked seizure[a]

Presenting seizure-type	Total	N (%) presenting as a first ever seizure
Simple partial	185	42 (22.7%)
Complex partial	265	76 (28.7%)
Secondarily generalized	467	310 (66.4%)
Absence	157	1 (0.6%)
Myoclonic	60	2 (3.3%)
Generalized tonic	3	2 (66.7%)
Generalized tonic–clonic	446	290 (65%)
Atonic	7	0 (0)
Epileptic spasms (West syndrome)	27	0 (0)
Convulsions, onset unclassifiable	325	203 (62.5%)

[a]Adapted from (CAROLE, 2000).

Age

Most of the literature is divided into pediatric and adult studies. As such, it is difficult to assess the difference, if any, between childhood and adult-onset seizures within a single study. In the two large randomized trials, a small effect was found for age in that children (<16 years) had a slightly higher risk of recurrence compared with adults (16–60 years) (First Seizure Trial Group, 1993). The other trial, although it contained a large number of children, did not report any significant effect for age at onset (Kim et al., 2006). Across observational studies, no compelling differences are seen that cannot be explained by variation in the distributions of symptomatic epilepsy and abnormal EEGs. Within a study, age typically has little if any influence on the risk of recurrence, and the occasional findings reported from single studies may simply reflect errors due to study-wise multiple testing.

Generalized versus focal seizures

Focal seizures may, at first glance, appear to be associated with a higher risk of recurrence; however, this is often because they are associated with symptomatic etiology as well as with abnormal EEG findings. Once these two main factors are considered, the evidence concerning an independent effect of partial versus generalized seizures is, at best, weak and variable (Annegers et al., 1986; First Seizure Trial Group, 1993; Bora et al., 1995; Stroink et al., 1998; Ramos Lizana et al., 2000; Kim et al., 2006). Still, an increased risk associated with partial seizures cannot be definitely excluded, particularly in individuals with a symptomatic first seizure (Hauser et al., 1990; Shinnar et al., 1996).

Type of seizure

Beyond the issue of generalized versus focal onset, there is no evidence strongly supporting the notion that specific types of seizures, if they present as an initial, first, unprovoked seizure, are associated with a greater or lesser risk of recurrence. In general, however, different seizure types are more or less likely to present with a first ever seizure. In particular, typical absence, myoclonic, and complex partial seizures as well as epileptic spasms are very unlikely to present as a first seizure. This tendency for certain seizure types to present with a first only versus with multiple seizures is beautifully demonstrated in the data from the French CAROLE study of patients with newly presenting seizures, both first and newly recognized epilepsy (Table 1) (CAROLE, 2000). The seizures most likely to present as a first seizure are generalized (including secondarily generalized) tonic-clonic seizures, ones with major motor manifestations that are hard to miss or to mistake for a passing odd behavior. Consequently, most of the literature on first seizures is either exclusively focused on patients presenting with tonic-clonic seizures or is heavily weighted toward that seizure type.

Complex seizure events: status epilepticus and multiple seizures in a single day

Traditionally, a complex event involving a very prolonged seizure or more than one seizure occurring within a 24-h period is still treated as a single event (Commission on Epidemiology and Prognosis and International League Against Epilepsy, 1993). For research purposes in epidemiology, status epilepticus is defined as a continuous seizure lasting at least 30 min or intermittent seizures without full return to baseline occurring over the course of at least 30 min. Status constitutes a neurological emergency and, at the time of the seizure, should be handled accordingly. Multiple distinct seizures within a 24-h period are also worrisome; however, they are generally considered as a single event the first time they occur (Commission on Epidemiology and Prognosis and International League Against Epilepsy, 1993). The concept of acute repetitive seizures (Mitchell, 1996), not quite continuous enough to constitute status and not discrete enough to be considered entirely separate seizures on a given day, is relatively new and not explicitly referred to in the first seizure literature;

however, it clearly has existed in the past and was either treated as status or as multiple seizures.

Because these are perceived as high-risk events, they are probably treated more often than simple single seizures (Loiseau et al., 1999). For the same reason, it is relatively unlikely that they would be included in a randomized trial in which they might risk being assigned to the untreated arm. In fact, they were explicitly excluded from the FIR.S.T study. Consequently, assessment of the prognostic value for recurrence of status epilepticus or multiple events in a single day is fraught with difficulties. That said, the evidence from available studies suggests that there is little if any additional risk of recurrence following one of these types of complex events in individuals with normal neurological exams (idiopathic/cryptogenic) (Hauser et al., 1990; Shinnar et al., 1996; Ramos Lizana et al., 2000; Kho et al., 2006). In one study primarily of adults, multiple seizures within a day or status epilepticus was associated with a substantially elevated risk of recurrence within the subgroup of patients with remote symptomatic first seizures (Hauser et al., 1990). One other study, reported in preliminary form, found an increased risk of recurrence associated with status epilepticus. For multiple seizures within a day, the overall findings did not suggest an increased risk; however, the specific findings varied by age of the patient with little effect in children and adults but a doubling of risk seen in the teen years (Loiseau et al., 1999).

Sleep state

Substantial evidence suggests that the risk of recurrence is greater if the initial seizure occurs during the asleep state (Hopkins et al., 1988; Bora et al., 1995; Shinnar et al., 1996; Ramos Lizana et al., 2000) although not all reports agree (Stroink et al., 1998). While first seizures that occur in the asleep state may be associated with a greater risk of recurrence, it is also possible that seizures that occur in sleep are not recognized as readily as those that occur during wakefulness. This raises the concern that a larger proportion of people presenting with a first seizure in sleep, versus while awake, may already have had one or more previous events (see predicting a second recurrence, below).

Family history

Certain types of epilepsy have a strong genetic basis and as such are associated with a greater likelihood of having a family member who has also had seizures. Whether this increases the risk of recurrence in someone who presents with a single seizure is not clear based on available evidence. At least three studies in children (Shinnar et al., 1996; Stroink et al., 1998; Ramos Lizana et al., 2000) and one in adults (First Seizure Trial Group, 1993) found little or no increased risk while a separate study in adults found a substantially increased risk (Hauser et al., 1990). Questions concerning this issue may require greater efforts to characterize the underlying disorder (i.e., epilepsy syndrome) for which the first seizure is the initial sign.

Prior febrile seizures

The relationship between febrile seizures and epilepsy is complicated. In some cases, a previous "febrile seizure" may really have been the first indication of epilepsy (Berkovic & Scheffer, 1998). This is particularly evident in Dravet syndrome, which, in three quarters of cases, initially presents as a convulsive febrile seizure (Panayotopoulos, 2005). These seizures are frequently prolonged. The phenomenon of febrile seizure plus (FS+) (Scheffer & Berkovic, 1997) is related to Dravet syndrome and underscores the complexity of this relationship and how ill-advised it would be, from a scientific standpoint, to insist on rigid artificial distinctions between febrile seizures and epilepsy. On the other hand, from a pragmatic standpoint and most especially for the purposes of counseling parents, the distinction is of tremendous utility.

Overall, the results across the literature concerning the prognostic significance of a history of previous febrile seizures in someone who presents with a first unprovoked seizure are mixed. There may be an increased risk of recurrence associated with previous febrile seizures in the group with remote symptomatic first unprovoked seizures (Hauser et al., 1990; Shinnar et al., 1996). In those with a cryptogenic first seizure, a history of febrile seizures seems less important although some increased risk cannot be ruled out (Hauser et al., 1990; Shinnar et al., 1996; Stroink et al., 1998; Ramos Lizana et al., 2000; Kim et al., 2006).

Other Seizure Outcomes

While a first recurrence is the most commonly studied outcome after a first unprovoked seizure, other outcomes are of equal or arguably even greater interest.

A second recurrence

In individuals who present at the time of a first seizure, those who experience a recurrence have a high likelihood of having further recurrences. In one prospective study largely of adults, the risk of a first recurrence was 21%, 27%, and 33% at 1, 2, and 5 years after the initial seizure. In those who recurred, the risk of a second recurrence was 57%, 61%, and 73% at 1, 2, and 5 years after the first recurrence. The risk of a second recurrence approached 90% in the remote symptomatic group and reached 60% in the cryptogenic/idiopathic group (Hauser et al., 1998). In a separate study exclusively in children, the risk of a second recurrence was 57%, 63%, and 72% at 1, 2, and 5 years after the first recurrence, almost identical to the risks seen in the adult study (Shinnar et al., 2000). Symptomatic etiology was the most salient predictor of a second recurrence (rate ratio = 1.69, CI 1.17–2.45, p = 0.005). Children whose first recurrence occurred within 6 months of

their initial seizure were also at substantially increased risk of a second recurrence compared to those children whose first recurrence happened later. The strength of the effect was similar to that for symptomatic etiology (rate ratio = 1.6, CI 1.14–2.26, p = 0.007).

This greater risk of further seizures in patients who have already had recurrent seizures is also clearly demonstrated in the MESS study in which patients with single seizures at the time of randomization had a much lower risk of a subsequent seizure compared with patients who had already had two or more seizures (Marson et al., 2005). In fact, it is, in part, this striking difference between the risk of a first recurrence versus the risk of a subsequent seizure in someone who has already had at least two seizures that has been used to support the distinction between first unprovoked seizure and newly diagnosed epilepsy. Finally, we should mention that other studies have shown overall higher remission rates in the long-term for individuals who present with a first seizure compared with those who present after having already had two or more seizures (Beghi & Tognoni, 1988; Hart et al., 1990).

Long-term remission

With half or more of individuals who present with a first seizure never having a recurrence, the remission rates tend to be quite high. The two large randomized trials already reviewed above demonstrate the point over a several year follow-up period. In the FIR.S.T study (Musicco et al., 1997), almost 90% of patients were at least 1-year seizure-free 4 years after enrolling in the study. The difference between the immediate and deferred treatment groups was on the order of a few percent and did not approach statistical significance. In the MESS trial, regardless of treatment policy, 92% of patients were at least 2-years seizure-free 5 years after enrolling in the study, findings that are highly comparable to those from the FIR.S.T trial (Marson et al., 2005).

Additional Considerations

A few issues are only occasionally raised in the first seizure literature but deserve to be mentioned.

Type of epilepsy

The French investigators eloquently made the point that all epilepsy starts with a first seizure and that it is therefore of value to consider the nature of the underlying disorder in a patient who presents with a first seizure regardless of whether the diagnostic term “epilepsy” is applied to the patient at that time (CAROLE, 2000). This recognition has also been the basis for recommendations regarding the use of neuroimaging in children presenting with a first unprovoked seizure (Hirtz et al., 2003), although it has perhaps of less value, at the present time, in adults. As more information becomes available about genetic determinants of specific forms of epilepsy, it is conceivable that, some time in the future, we will be able to identify diverse specific forms of epilepsy from the initial seizure and tailor evaluation, treatment, and management plans accordingly.

Characterization of risk factors

The primary risk factors for recurrence have tended to be bluntly defined: symptomatic epilepsy or abnormal EEG. More detailed characterization of these factors might possibly result in greater predictive value, both positive and negative.

Consequences versus probability of a recurrence

As will be further discussed in this issue, the risk of recurrence is only one piece of information needed when making recommendations and decisions regarding further treatment and management. Two additional factors that merit being raised in the context of seizure recurrence per se are status epilepticus and sleep state.

Status epilepticus

Although status epilepticus itself does not appear to be a major risk factor for recurrence, an individual who had status as a first seizure or one of the first seizures is at much greater risk of having a recurrent episode of status should he or she have another seizure (Berg et al., 2004). For this reason, the actual probability of recurrence must be viewed not just as the probability of another seizure but the probability of another very prolonged seizure. This, of course, may push treatment decisions toward rather than away from treatment. It should certainly influence the counsel presented to the patient and family.

Sleep state

Although most evidence suggests that a first seizure that occurs during sleep has an increased risk of recurring, there is a tendency for someone whose first seizure occurred in sleep to have recurrent seizures during sleep. Thus, the higher risk is somewhat mitigated by the low risk consequences of the circumstances. In fact, in some states in both the United States and the European Union, people with active epilepsy may drive if their seizures reliably occur during sleep (Krauss et al., 2001; Beghi & Sander, 2005). This once again touches on the issue of specific epilepsy syndromes some of which are known to have striking nocturnal patterns of occurrence. One such syndrome is autosomal dominant, nocturnal, frontal lobe epilepsy (ADNFLE) (Scheffer et al., 1994, 1995).

Summary and Conclusions

Further factors influencing the recommendations and decisions to treat someone who presents with a first seizure are discussed in later sections of this issue. This review has examined the statistical risk of a recurrent seizure, the time period over which that risk is expressed, and major factors influencing the risk as well as subsequent seizure

outcomes. Treatment can decrease the risk of a recurrence. Symptomatic etiology and abnormal EEG findings are the two most consistent known predictors of seizure recurrence and can be used to identify groups with very high (>60 or 70%) versus moderately low (<30%) risks. Overall, the long-term outcome in terms of complete seizure control is excellent with the vast majority of patients (about 90%) becoming completely seizure-free.

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