# LONG-TERM OUTCOMES OF CHILDHOOD EPILEPSY: "THE TRUTH IS RARELY PURE AND NEVER SIMPLE"[1]

**Natural History of Treated Childhood-Onset Epilepsy: Prospective, Long-Term Population-Based Study**

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*Brain* 2006;129(Pt 3):617–624

It is not well known how often drug resistance, a major clinical problem, occurs early or late in the course of epilepsy and how often epilepsy follows a continuous, remitting or relapsing-remitting pattern. To provide evidence if, in fact, different patterns of evolution of drug resistance and remission exist, a prospective, long-term population-based study of 144 patients followed on the average for 37.0 years (SD 7.1, median 40.0, range 11–42) since their first seizure before the age of 16 years was performed. At the end of follow-up, 67% of 144 patients were in terminal remission, on or off antiepileptic drugs. Early remission, starting within the first year of treatment, was seen in 45 patients (31%). In 23 (16%) of them, first remission continued, uninterrupted by relapse, to terminal remission. Late remission with a mean delay of 9 years was achieved by a further 72 patients (50%), including 46 (32%) patients who achieved terminal remission without any relapse and suggested, together with 23 patients, a remitting course. Following a relapse after early or late remission, 28 (19%) patients achieved terminal remission, suggesting a remitting-relapsing pattern. Altogether 20 patients (14%) did not re-enter remission, indicating a worsening course of epilepsy. Twenty-seven (19%) patients were drug-resistant from the start to the end of follow-up. In conclusion, half the patients with childhood-onset epilepsy will eventually enter terminal remission without relapse and a fifth after relapse. One-third will have a poor long-term outcome in terms of persistent seizures after remission or without any remission ever.

## COMMENTARY

Treatment decisions in clinical practice are based on assumptions of the long-term prognosis of a patient's epilepsy. For example, a large body of literature characterizing factors that predict recurrence after a first seizure can be used to identify those patients who should receive antiepileptic medication. Another key step in clinical decision making is the declaration that a patient's epilepsy is medically intractable. This determination has profound implications for future life quality and is a prerequisite to considering epilepsy surgery. Can determination of medical intractability be made in an early, timely, but accurate fashion?

The complexity of identifying medical response and intractability is revealed by Sillanpää and Schmidt in this thoughtful analysis of a uniquely valuable dataset. Ascertainment of every patient with epilepsy onset prior to age 16 in the catchment area of the University of Turku, Finland was made in the 1960s. These 245 patients were prospectively examined and evaluated at intervals by Dr. Sillanpää. Ninety-five patients were not included because they initially had been evaluated before the study onset in 1961, and six were excluded because they had less than 10 years of follow-up, leaving 144 patients in this study. The complete cohort of 245 patients has been discussed in a prior manuscript (2).

Remission was defined as 5 years free of seizures, on or off medication. Echoing numerous past studies, two-thirds of the patients ultimately became seizure free and 19% never had a remission. The most valuable findings, however, concern the fact that the majority of patients have a prolonged and often relapsing and remitting course, with only a small minority achieving an early (i.e., within the first year) permanent remission. Of the 45 patients (31%) with early remission, 22 (15%) relapsed, but ultimately a total of 37 (27%) of the early remission

Epilepsy Currents, Vol. 6, No. 6 (November/December) 2006 pp. 181–183
Blackwell Publishing, Inc.

group achieved terminal remission. The most interesting group is the 72 patients (50%) with late remission. Even though 26 (18%) had one or more relapses, ultimately 60 of this late remission group (42%) achieved terminal remission. The reader is referred to Figure 2 of the manuscript, which presents the complex portrait of outcomes in these patients. Etiology was a significant predictor of outcome—patients with symptomatic epilepsy were less likely to achieve terminal remission. IQ of 70 or less also predicted a significantly worse seizure outcome. Although there was a trend for a poorer outcome in presumed temporal lobe and Lennox-Gastaut patients, numbers were too small to analyze.

The work by Sillanpää and Schmidt gives new insight into the burden of epilepsy on individuals and society. Even though the majority of patients will reach a state of long-term control, most will experience years of medications and intermittent seizures on the road to that outcome. It is the fear of relapses and their commonness that may explain why it is that only patients in long-term remission, off medications, display nearly normal quality-of-life measures (3). The fortunate patients with early and permanent seizure control are a distinct minority.

Although this is a landmark study, nonetheless, there are unavoidable limitations to its application to clinical decisions. Of course, it does not address adult-onset epilepsy, which could have differences in outcomes. Another study limitation is that treatment options have changed since the 1960s and 1970s—for example, no patient in this study received epilepsy surgery. These differences in treatment choice possibly could lead to modest changes in outcomes. The most important limitation is that the reasons for relapse are not characterized in this article—indeed, it may be difficult to objectively determine the reasons in some patients. While it may be tempting to equate relapse or lack of remission with intractability, doing so often may not be appropriate. For example, it is plausible that after years of seizure control, medication may be withdrawn or a patient's compliance may falter, and these events may lead to seizure recurrence. In many cases, the seizure recurrence would not demonstrate intractability but rather either a requirement for medication for seizure control or a transient, self-limited response to medication withdrawal.

Fortunately, in a companion article, the authors had addressed the issue of medication withdrawal in this same cohort (4). Withdrawal of medication was proposed in children less than 15 years of age who were seizure free for 2–3 years and for older patients who were seizure free for 5 years. However, the process was not random; for instance, withdrawal was typically not suggested for patients with juvenile myoclonic epilepsy. Medication withdrawal was attempted by 90 of the 148 patients, and an additional 14 patients achieved terminal remission but did not attempt medication withdrawal (4). Of the 90 patients, 81 ultimately did achieve terminal seizure remission without medication, but 33 of the 90 suffered a relapse during this process. Two relapsing patients regained seizure control on medication; 24 relapsing patients achieved terminal remission without needing to restart medication, but the 7 remaining patients have persisting seizures, with 6 continuing antiepileptic medication. This supplemental study indicates that the majority of patients ultimately achieve a lasting seizure and antiepileptic-medication-free state and that seizure occurrence as medication is tapered, does not necessarily preclude successful withdrawal. Moreover, the companion article reveals that a significant minority of seizure relapses reported in the present study occurred during deliberate medication withdrawal and such seizures typically do not indicate intractability.

What are the implications of these data for current concepts of medical intractability? One concept is that intractability can be predicted according to the response to initial systematic medication trials (5). The occurrence of late initial remissions in 50% of the patients appears to be at odds with the possibility of reliable early identification of intractability. However, such a conclusion would be based on the assumptions that the initial interventions were appropriate, timely, and rapid and that the late onset of remission was not due to delay in institution of an appropriate regimen. Further analysis of the dataset by Sillanpää and Schmidt could clarify the reasons for a later initial remission. Even if further study confirmed that initial remission in many patients takes longer to achieve than previously assumed, it still is quite likely that certain clinical characteristics—such as epilepsy syndrome, etiology, and seizure frequency, in combination with response to initial medication trials—could ultimately prove to be reliable predictors of long-term intractability in a patient subgroup. A second current concept regarding medical intractability is that it may develop many years after the initial onset of the epilepsy (6). Among the Turku patients, 20 of the 117 patients who achieved an initial 5-year remission had a relapse and then never attained a terminal 5-year remission. The existence of this group supports the hypothesis of late development of intractability, but more information on the medication trials used would be needed to confirm the finding.

The current study, therefore, suggests that both concepts of intractability are correct for the appropriate patient subgroup: intractability occurs early and persistently in 19% of patients and late, after relapse, in 14%. This meticulous and thorough analysis yields no simple answers. The outcomes are complex and varied, as would be expected from the heterogeneous nature of the epileptic condition.

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