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# Natural history of treated childhood-onset epilepsy: prospective, long-term population-based study

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**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.**

**Keywords**: pharmacoresistance; drug resistance; antiepileptic drugs; clinical patterns; remission

**Abbreviations**: AEDs = antiepileptic drugs

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## Introduction

During treatment with a variety of different antiepileptic drugs (AEDs), as many as 20–40% of newly treated patients with epilepsy will not enter long-term remission for several years (Annegers *et al.*, 1979; Cockerell *et al.*, 1995; Kwan and Brodie, 2000). Despite state-of-the-art medical management with modern AEDs, most of these patients continue to have drug-resistant epilepsy with frequent debilitating seizures and severe consequences such as increased mortality (Schmidt, 2002; Sperling, 2004). Considering that epilepsy is one of the most common chronic neurological disorders, drug-resistant epilepsy is a major public health problem. One concern why current AEDs do not seem to prevent or reverse drug resistance in most patients is that we may have missed the optimal time for intervention because we do not know when drug resistance manifests itself in the course of epilepsy (Schmidt and Rogawski, 2002). In addition, emerging evidence suggests that different neurobiological mechanisms may possibly contribute to various patterns of drug resistance (Schmidt and Löscher, 2005). Finally, knowing that drug resistance occurs in different clinical patterns would be useful for patient counselling and planning of intervention trials tailored to different temporal patterns of drug resistance in patients with epilepsy, if they exist.

More specifically, three hypotheses co-exist based on retrospective observations of the evolution of drug resistance as measured in the time to onset of intractability (Goodridge and Shorvon, 1983; Camfield *et al.*, 1997; Kwan and Brodie, 2001; Berg *et al.*, 2003; Berg, 2004). First, based on retrospective or partly prospective and hospital-based observations, at least in part, in adult-onset epilepsy, it has been claimed that in most

cases pharmacoresistance is constitutive, i.e. it has been fully developed before the first seizure or at least before the start of AED treatment (Kwan and Brodie, 2000). However, contrary to the prevalent assumption that refractory epilepsy always announces itself as refractory from the onset, mounting evidence indicates that this may not always be the case, and a number of patients do develop pharmacoresistant epilepsy after responding well to early AED treatment. This leads to the second hypothesis. There is emerging evidence from one retrospective study of a highly selected group of patients undergoing temporal lobe surgery that, at least in some patients with easily treatable epilepsy, pharmacoresistance requiring surgery develops years later in the course of their epilepsy (Berg *et al.*, 2003). Other suggestive evidence that drug resistant epilepsy may be a progressive condition has been summarized recently (Kwan and Brodie, 2002). Finally, the third hypothesis claims that drug resistance may remit and reappear in the course of epilepsy or its treatment. Goodridge and Shorvon (1983) described an intermittent pattern where active epilepsy is interrupted by periods of remission. Although relapse is not equivalent to drug resistance, and no information was made available on how often relapse of seizures was due to drug withdrawal, these data suggest that in some patients pharmacoresistance may be reversible, at least for a period of several years. Findings from randomized placebo-controlled add-on trials also indicate that a small percentage of patients with previously drug-resistant partial epilepsy will respond to become seizure-free during trials of new AEDs (French *et al.*, 2004). The purpose of the present study was to examine if different evolutionary patterns of intractability in fact exist in a large prospective population-based series of patients with childhood-onset epilepsy when drug-resistant epilepsy often begins (Schmidt and Löscher, 2005), followed for several decades since the onset of their epilepsy.

## Methods

### Patients

The study subjects included all children aged 15 years or less who were living in the catchment area of University of Turku Central Hospital, Turku, Finland, at the end of 1964 and who met the criteria for epilepsy (two or more unprovoked seizures) (Commission on Classification and Terminology of the International League against Epilepsy, 1981; Central Statistical Office of Finland, 1989; Commission on Epidemiology and Prognosis of the International League against Epilepsy, 1993). Subjects were identified on the basis of hospital, institution and primary health care records, and a review of the National Health Service records, a registry of all patients residing in Finland. Altogether, 245 patients were identified, 223 (91%) of them were seen in the University of Turku Central Hospital. The remaining 22 patients (9%) were seen in other hospitals, institutions, and public or private primary or outpatient care offices. In Finland in the 1960s, the rule was that children with an epileptic seizure were referred for evaluation. Untraceable and subsequently beyond the study remained only three more patients who, in an ongoing surveillance, were identified and who met the inclusion criteria. Thus, the patient sample represents a population-based cohort of children aged 0–15 years with epilepsy.

The 245 patients included 150 (61%) patients with incidence cases, i.e. they were first evaluated for epilepsy from January 1, 1961 to December 31, 1964. The remaining 95 patients (39%) had been seen for epilepsy both before and during the study period of 1961–1964. They had had at least one seizure in the preceding 3 years before the evaluation during the study period (prevalent cases). All 245 patients were examined and evaluated by one child neurologist, (Sillanpää, 1973) enrolled in a prospective follow-up of medical and social outcomes for an additional 35 years. Follow-up included ongoing review of the medical records and a comprehensive evaluation with 5-year intervals. In 1992, in addition to the structured extensive questionnaires, the evaluation included clinical examination completed with appropriate tests for physical fitness and laboratory investigations. The study design and some earlier results have been reported in detail previously (Sillanpää *et al.*, 1998, 1999, 2004; Sillanpää, 2002).

For the present study, patients who had been followed since the onset of epilepsy (incident cases), were included. Of these 150 patients, six (4%) were excluded due to less than 10-year follow-up. Thus, the remaining 144 (96%) constitute the present population-based study cohort. They had been followed on the average for 37.0 years (SD 7.1, median 40.0, range 11–42).

### Definitions

Epileptic syndromes, epilepsies, epileptic seizures and aetiology of seizures were defined according to the guidelines for epidemiological research of the International League Against Epilepsy (Commission on Classification and Terminology of the International League Against Epilepsy, 1981; Central Statistical Office of Finland, 1989; Commission on Epidemiology and Prognosis of the International League Against Epilepsy, 1993). Random generalized epilepsy was defined as epilepsy with generalized tonic-clonic seizures randomly distributed during the sleeping–waking cycle as described by Janz (1969). Remission of epilepsy was defined as a seizure-free period of 5 or more consecutive years as suggested in the literature (Annegers *et al.*, 1979). Terminal remission was the term used for remission at the end of follow-up. Remission and terminal remission, if any, were achieved either early, i.e. within 12 months of starting treatment, or late, i.e. after more than 1 year of treatment. Terminal remission could be uninterrupted from the start of treatment to the end of follow-up (remitting course) or be interrupted by relapse (remitting–relapsing course). Remission could be followed by reappearance of seizures without any further terminal remission (worsening course). Epilepsy was called drug-resistant, if remission was not achieved during a follow-up of at least 10 years despite adequate treatment. Relapse was defined as the occurrence of repeated seizures after a patient had entered remission of 5 years or more. Relapse was also considered in conjunction with planned discontinuation of AEDs in patients in remission. A single seizure, however, including those prompted immediately by drug withdrawal, poor compliance or one occasion-related seizure was not classified as a relapse. Accordingly, patients with a single seizure continued to be classified as being in remission. Compliance was determined by questioning the patient. Compliance was termed good if the patient answered: 'Yes, according to the given instructions' to the question: 'Have you taken your drugs regularly?'. The other options were: 'Yes, regularly, but less than instructed'; 'I have occasionally forgotten medication'; 'I have taken the medication

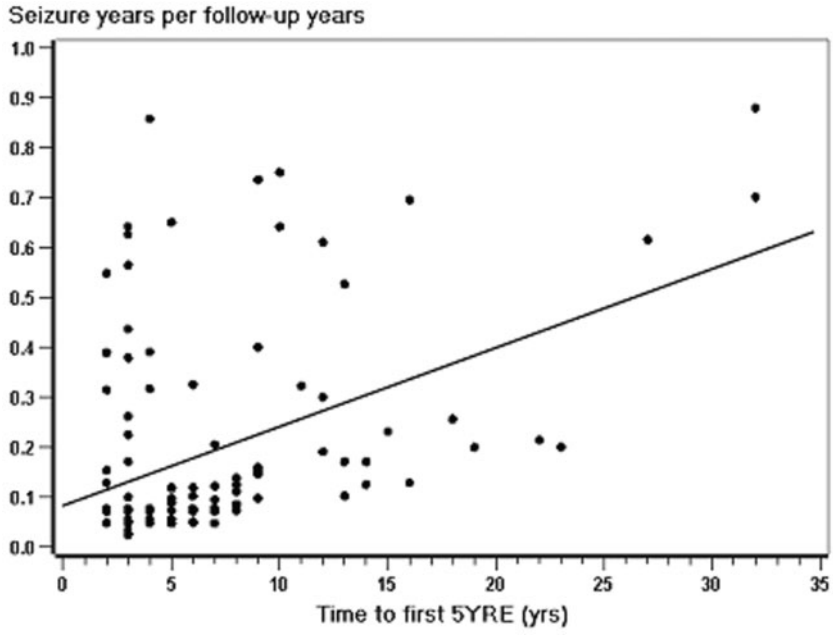


**Fig. 1** Number of years preceding the first 5-year remission ever (5YRE) correlated to the proportion of seizure-years per all pre-remission years ($r = 0.44091$, $P < 0.0001$). The data indicate that the more pre-remission years were seizure-years, the longer it took to achieve 5-year remission.

irregularly'; 'There have been longer breaks in the medication'; 'I have spontaneously discontinued the medication'.

### Statistical analysis

For statistical analyses, Pearson's $\chi^2$-test with Fisher's exact test (two-tail) and Yates's correction when appropriate, Student's *t*-test, Mann–Whitney test, Kruskal–Wallis test, and stepwise and cumulative stepwise logistic regression analyses were used. A *P*-value of <0.05 was considered statistically significant. Statistical computations were done using SAS System for Windows, release 8.02 (SAS Institute, Cary, NC, USA). The study design was approved by the Joint Ethics Review Committee of the University of Turku and the University Central Hospital of Turku.

## Results

### Long term seizure outcome

At the end of the 37-year follow-up (SD 7.1, median 40.0, range 11–42), 97 (67%) of 144 patients were in terminal remission, 14% of 97 on AEDs and 86% off AEDs, while 33% of 144 either never experienced any 5-year remission (i.e. were drug-resistant, 19%) or were not in terminal remission (but had previously had one or more 5-year remissions, 14%).

### Time to remission

Among 117 out of 144 patients, who entered at least one remission period (i.e. 27 drug resistant patients excluded), the higher the proportion of years with seizures per follow-up years, the longer did it take to arrive at the first 5-year remission, if ever (Fig. 1). In logistic regression analysis, the higher the number of years before entering 5-year remission, the higher was the annual risk of relapse (odds ratio increased from 1.004 in the first pre-remission year to 1.020 in the fifth year, but the increase was not significant).

### Early remission

Remission was reached within the first year of treatment in 45 patients (31%) (Fig. 2).

Despite a good initial outcome, a relapse occurred in 22 patients who will be discussed below in more detail (Fig. 2). The remaining 23 patients went into terminal remission without a relapse up to the end of follow-up of 26–42 years (mean 39.1 ± 4.1, median 41.0). All of them were without medication at the end of follow-up. Medication was discontinued in 57% of patients within 1 year, and in 91% within 4 years. Two patients continued treatment further, one for 19 years, the other one for 28 years.

### Late remission

Seventy-two patients of 144 (50%) entered late remission, i.e. within 4–32 years of follow-up (mean 9.2 ± 6.2, median 7.0). One or more relapses were noted in 26 patients, but 46 remained in terminal remission without any relapse (Fig. 2). The 46 patients who achieved terminal remission without a relapse did so with a delay of 4–23 years (mean 8.5 ± 4.9, median 7.0). Thirty-five patients achieved terminal remission within 4–9 years, nine patients within 10–19 years, and the remaining two patients within 20–23 years. Until the

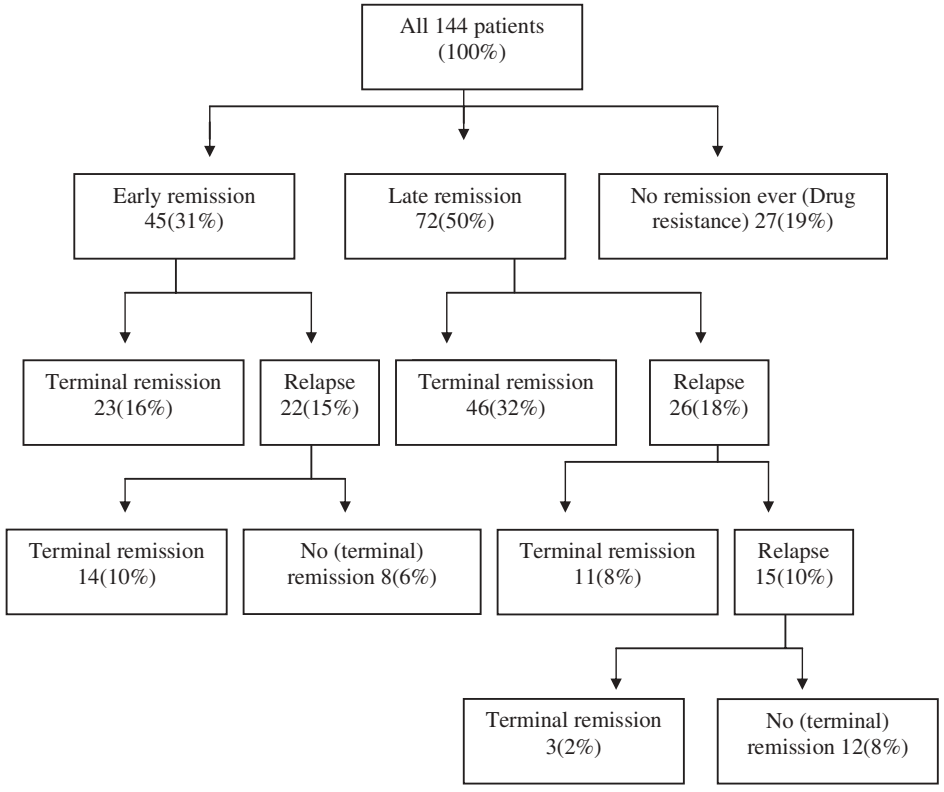


**Fig. 2** Patient disposition and outcome chart. Remission = seizure freedom of ≥5 years; early remission = remission within 12 months of treatment; late remission = remission after 12 months of treatment; terminal remission = remission at the end of follow-up; relapse = two or more seizures after remission; drug resistance = no remission ever.

end of follow-up, the terminal remission had lasted 7–39 years (mean 31.11 ± 7.4, mean 34.0), from 7 to 20 years in 4 patients, 11–30 years in 12 patients, and from 31 to 39 years in the remaining 30 cases. At the end of follow-up, 5 of 46 patients were on medication and 41 off medication.

## Remitting course of epilepsy

Terminal remission uninterrupted by relapse was noted in 23 patients after entering early remission, and in further 46 patients following late remission, resulting in a total 69 (48%) of 144 patients with a remitting course of epilepsy (Fig. 2).

## Remitting–relapsing course of epilepsy

In 48 (33%) of 144 patients, remission was followed by one or more relapses, suggesting a remitting–relapsing course of epilepsy (Fig. 2). The first relapse occurred within 7–33 (mean 13.5 ± 7.3, median 10.5) years among the early remitting patients and within 9–39 (mean 20.4 ± 9.6, median 17.5) years in the late remitting patients ($P$ = 0.0019). Terminal remission after relapse was noted in 14 of 22 patients in the early remission group, and in 14 of 26 patients in the late remission group (Fig. 2). Relapse was seen in conjunction with planned discontinuation of AEDs in five patients. The 20 patients who did not enter remission after relapse will be discussed below.

## Worsening course of epilepsy

Altogether 20 (14%) of 144 patients—8 of 45 patients with a sequence of early remission followed by relapse and 12 of 72 with late remission followed by relapse—never regained terminal remission (Fig. 2). The risk for failing to enter terminal remission after relapse was not higher in the late versus the early remitting group (RR 1.05; 95% CI 0.58–1.90; $P$ = 0.8766). Also, time from first relapse did not differ between the early and late remission groups ($P$ = 0.3224). When 20 patients who never entered terminal remission after relapse were compared with the 97 patients who gained terminal remission during follow-up, stepwise logistic regression showed that symptomatic aetiology of seizures (versus idiopathic or cryptogenic aetiology), was the only predictor of failure to enter late terminal remission after previous remission (OR 8.2, 95% CI 2.7–24.8, $P$ = 0.0002). However, no significant association was found with mental level ($P$ = 0.0931), localization-related epilepsies ($P$ = 0.2193) or temporal lobe epilepsy ($P$ = 0.6204). Neither had they any progressive brain process, except for one who had initially simple partial seizures of 'limbic seizure type' and EEG with generalized discharges at age 1 year in 1961. After a good early response to drug therapy and subsequent remission of 22 years, he started to have seizures in 1983. Cranial computed tomography then revealed typical signs of tuberous sclerosis. Since that time, he has had persistent seizures.

**Table 1** Drug resistance and worsening course in childhood-onset epilepsy during long-term follow-up epilepsy by syndrome

| Epilepsy syndrome | Drug resistance *N* | Remission progressing to no remission *N* | Terminal remission *N* | All *N* |
|---|---|---|---|---|
| Localization related | 18 | 11 | 57 | 86 |
| Idiopathic | 1 | 0 | 13 | 14 |
| Rolandic | 1 | 0 | 13 | 14 |
| Symptomatic | 15 | 11 | 39 | 65 |
| Temporal lobe | 12 | 8 | 23 | 43 |
| Frontal lobe | 1 | 0 | 2 | 3 |
| Occipital lobe | 0 | 0 | 2 | 2 |
| Not localizable | 2 | 3 | 12 | 17 |
| Cryptogenic | 2 | 0 | 5 | 7 |
| Generalized | 9 | 7 | 29 | 45 |
| Idiopathic | 2 | 2 | 27 | 31 |
| Childhood absence | 1 | 0 | 4 | 5 |
| Juvenile absence | 1 | 1 | 0 | 2 |
| Juvenile myoclonic | 0 | 0 | 1 | 1 |
| Awakening | 0 | 0 | 6 | 6 |
| Random generalized | 0 | 1 | 14 | 15 |
| Other primary generalized | 0 | 0 | 2 | 2 |
| Cryptogenic and/or symptomatic | 7 | 5 | 2 | 14 |
| West syndrome | 5 | 3 | 0 | 8 |
| Lennox–Gastaut syndrome | 2 | 2 | 2 | 6 |
| Undetermined whether focal/gener'd | 0 | 1 | 3 | 4 |
| Unclassifiable | 0 | 1 | 8 | 9 |
| All (%) | 27 (19%) | 20 (14%) | 97 (67%) | 144 (100%) |

Drug resistance was defined as having no 5-year remission period during follow-up.

Eight of 20 patients (5.6% of 144 patients) who had entered early remission within 1 year, were in remission for 6–18 years before having a relapse on medication (Fig. 2). They all had entered within 1 year 5- to 20-year remission. All but one of eight patients had typically experienced, as a 'warning sign', a few seizures before four of them again remitted for 5–12 years. After the second remission period, two patients had a third relapse. After the latest relapse, all patients continued to have seizures. Twelve of 20 patients who failed to enter terminal remission after late remission during a follow-up of 3–31 years had one relapse and two of them two relapses (Fig. 2). The first relapses appeared within 5–8 years except for two patients whose relapse occurred 18 and 35 years after onset of the first remission, respectively.

## Drug resistance

Drug resistance, i.e. no remission period ever on continuing AED therapy occurred in 27 of 144 (19%) patients (Fig. 2). The follow-up was, on the average, 29.9 years (SD ±11.3, median 32, range 11–42). Out of 27 patients 12 had more than one seizure every year, 8 patients had on the average one seizure per year and in the remaining 7 patients was observed one seizure every 1.1–5.0 years. None of the drug-resistant patients underwent surgery for epilepsy. We checked compliance (*see* definition) after 10, 15, 20 and 25 years of follow-up. There was no significant difference in compliance between seizure-free patients and drug-resistant patients; compliance was even better in the drug-resistant than in seizure-free patients (83 versus 75%).

Table 1 shows the distribution of drug resistance by epilepsy syndrome. Drug resistance was most common in temporal lobe epilepsy and in the West syndrome-Lennox–Gastaut complex. The proportion of drug-resistant cases was highest in generalized symptomatic/cryptogenic epilepsies (7 out of 14 patients), followed by localization-related symptomatic epilepsy (15 out of 65 patients), and lowest in idiopathic generalized or and localization related epilepsies (1 out of 14 and 2 out of 31 patients, respectively). Accordingly, the risk of drug resistance was higher in symptomatic than in idiopathic epilepsies, whether localization-related or generalized [relative risk (RR) 4.33, 95% CI 1.66–11.32, $P = 0.0016$]. The numbers became too small for further analysis of individual epilepsy syndromes (Table 1). Risk factors for drug resistance over all epilepsy syndromes, including localization-related, generalized, undetermined whether localization-related or generalized and unclassifiable epilepsies, were mental retardation, with an IQ of 70 or less (RR 2.79; 95% CI 1.83–4.24, $P < 0.0001$), and symptomatic aetiology (RR 2.22; 95% CI 1.61–3.05, $P < 0.0001$).

## Discussion

The main results of this prospective, long-term population-based study of 144 adult patients followed since their first seizure, before age 16, were: one, at the end of the mean follow-up of 37 years, 67% of 144 patients were in terminal remission, while 33% were not in remission, including 19% who were drug-resistant from the start and, according to our

definition, never entered 5-year remission during follow-up. Two, among the 67% in terminal remission, 16% of patients achieved uninterrupted seizure freedom early in the course of treatment, within 12 months. A further 51% eventually achieved terminal remission with a delay after failure to enter early remission. Although it is reassuring that in total 67% of patients were able to enter terminal remission, it may take more than a decade in many patients, particularly in those with mental retardation and symptomatic epilepsy. Three, 48 (33%) regained remission after relapse, including 28 patients (19%) with terminal remission, suggesting a remitting–relapsing pattern. Finally, 20 patients (14%), failed to regain remission after relapse suggesting a progressively worsening course of epilepsy.

The implications of these results are, in our view: one, that in patients with childhood-onset epilepsy, long-term seizure outcome cannot be reliably determined by the response at the onset of treatment. Early remission does not guarantee terminal remission, which occurred in 23 of 45 patients (51%) in our series. Nor does early failure to enter early remission predict a poor long-term outcome. Terminal remission was preceded by late remission in 60 of 72 patients (83%). Two, although mental retardation and symptomatic aetiology are overrepresented in those with drug resistance, in the long run, a proportion of patients as high as 61% with mental retardation and symptomatic aetiology will eventually enter remission, and 35% of patients may benefit from terminal remission. However, it may take many years until remission or terminal remission is seen. Three, the aetiology of the epilepsy syndrome is an important guide for outcome. Symptomatic, localization-related and generalized epilepsies proved to be more often drug-resistant than idiopathic, localization-related and generalized epilepsies. In accordance, idiopathic epilepsies, either generalized or focal, did have the best outcome both for early and late-onset remission. The literature on clinical patterns and dynamic evolution of drug resistance has been briefly reviewed in the introduction and in more detail in a recent review (Schmidt and Löscher, 2005). Unfortunately, our current understanding of the putative mechanisms of drug resistance is too incomplete for examination of syndrome-specific mechanism of drug resistance, if they exist (Schmidt and Löscher, 2005). From a clinical perspective, however, four questions can be addressed. One, is initial failure to enter remission predictive of long-term drug resistance?; two, is initial failure to reach remission reversible in the course of the disorder?; three, is there a progression from remission to no remission?; and four, how common is a remitting–relapsing pattern of epilepsy?

## Is initial failure to enter remission predictive of long-term drug resistance?

Our results indicate that initial success or failure to enter remission is not a reliable indicator of long-term success or failure to achieve remission. In support of our data, Camfield *et al.* (1997) found that response to the first AED was only broadly predictive of outcome in 417 children treated for epilepsy. In 345 children responding to the first AED, 61% eventually went into remission. In fact, 30 of 72 (42%) who failed to respond to the first AED later achieved remission suggesting that initial drug response is no reliable predictor for drug resistance. In agreement with Camfield's data, our series shows *de novo* drug resistance, defined as no remission ever, in only 19 per cent (27 out of 144) of all patients. Our results support a concept of a more dynamic and, incidentally, beneficial evolution of the disorder in most patients with childhood-onset epilepsy. Most patients with initial failure to reach remission in our prospective series subsequently turn out to enter terminal remission or remission later in the course of the disorder.

## Is initial failure to reach remission reversible?

That previously pharmacoresistant epilepsy, by any definition, can be attenuated, at least in part and transiently, is a well-known fact in a single-digit number of patients entering placebo-controlled randomized trials where add-on treatment with a modern AED achieves short-term seizure control for usually 1 month. This figure, however, does not represent the likelihood of patients remaining seizure-free over a long-term period (French *et al.*, 2004). In our long-term population-based study, most patients (51%) who achieved remission also remained in terminal remission suggesting a remitting course. However, it may take on the average >9 years in half of those patients until terminal remission is finally achieved. In our series, the time to reach remission was longer in those with a history of frequent seizures as measured in number of years in which seizures occurred. Furthermore, it is tempting to speculate that one reason why it took so long to reach remission in our study population is that although most of our patients were treated with carbamazepine and valproate, valproate was not available initially. However, valproate was available and increasingly used since 1971 in the Turku area before it was registered in 1973 for all of Finland. Furthermore, none of our patients underwent epilepsy surgery. If one would repeat our study in children now started on newer AEDs, remission might be reached faster and many patients with drug resistance could benefit from surgery with as many as two of three entering 5-year remission on or off medication (Schmidt *et al.*, 2004). However, there is no compelling evidence that currently used newer AEDs are more efficacious (Schmidt, 2002) and the results of such a repeat study, if started today, would be available only 30 years from now.

## Is there a progression from remission to no remission?

Only 5.6% of the patients entering early remission turned out to be unable to regain remission after a relapse. Mental retardation and symptomatic aetiology in particular may be associated with progressive development of drug resistance. In a

Canadian study of children, 4% of patients did develop pharmacoresistant epilepsy after having responded well to the first AED (Camfield *et al.*, 1997). Two, according to one, albeit retrospective observation, a substantial proportion of localization-related epilepsies may not become clearly pharmacoresistant for many years after onset (Berg *et al.*, 2003). In the analysis of Berg *et al.* (2003), a prior remission of 5 years or longer was reported by 8.5% of surgical candidates with pharmacoresistant epilepsy. The time to pharmacoresistance may be several years and extend to >10 years, especially if the onset is during childhood.

## How common is a remitting–relapsing pattern of epilepsy?

In 28(19%) of 144 patients, remission was followed by relapse(s) and return to terminal remission suggesting a remitting–relapsing pattern of epilepsy. In their description of patterns of remission, Goodridge and Shorvon (1983) noted in 12% of their patients an intermittent pattern where active epilepsy is interrupted by periods of remission. They defined remission as a period of freedom of seizures of 2 years or more. Unfortunately, important information is missing, such as whether seizure relapse was due to drug withdrawal and how often patients with relapse seizures could be controlled again. Our data suggest that in some patients failure to enter remission may be reversible, at least for a period of several years.

Although no claim can be made or is intended that AEDs are involved in reversing drug resistance, our data show that any theory for pharmacoresistance needs to take into account that failure to enter remission may be progressive or reversible in some patients with childhood-onset epilepsy (Schmidt and Löscher, 2005). However, relatively few patients (27 of 144 in our series) were drug-resistant and only 20 (14%) of 144 patients progressed from remission to no remission. Morphological and functional alterations in brain targets and epileptic circuits have been implicated with progression of epilepsy despite AED treatment (Schmidt and Rogawski, 2002; Pitkänen and Sutula, 2002; Walker *et al.*, 2002). Hypothetically, putative neurobiological mechanisms of pharmacoresistance may be different in patients who have never responded to an AED versus those who progressed to pharmacoresistance after they responded initially to therapy. In addition, the mechanisms of reversing pharmacoresistance may differ from those generating pharmacoresistance. However, a competing explanation is that the improvement after initial failure to respond may be also related to changes in AED use, for example the introduction of newer drugs, over the years.

### *Limitations of Study*

The main limitations of our long-term study is that the numbers of patients are relatively small, and we cannot discern impact of natural history and specific effects of medical treatment or individual AEDs. Also, our study is limited to adults with childhood-onset epilepsy and our findings cannot be directly extrapolated to studies with epilepsies which manifest themselves first in adulthood. However, studies of drug resistance and remission in adults with childhood-onset epilepsies may be particularly useful, as many, if not most adults with drug-resistant epilepsy have their disorder since childhood (Schmidt and Löscher, 2005). To compare our long-term results with a follow-up of 35 years directly to adult-onset epilepsies one would need a study in the middle to old age range with early adulthood-onset epilepsy. Such a study does not exist. Also, we need to mention that definitions vary in the literature and many of the data in the literature stem from retrospective studies and thus are difficult to compare in detail with our results.

## Conclusions

In conclusion, our data suggest that the natural history of drug resistance and remission is much more complex and dynamic than previously thought. An array of diverse dynamic changes occurs; most patients who failed to enter remission at the start will achieve terminal remission. In a small minority, epilepsy will become worse, or will form a remitting–relapsing pattern. It is not unreasonable to consider that different mechanisms and hopefully options for interventions exist when patients with these different forms of drug resistance and remission are examined more closely in future clinical and pharmacological studies.

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