Original article

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Time to relapse after epilepsy surgery in children: AED withdrawal policies are a contributing factor

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ABSTRACT – *Aim*. It was recently suggested that early postoperative seizure relapse implicates a failure to define and resect the epileptogenic zone, that late recurrences reflect the persistence or re-emergence of epileptogenic pathology, and that early recurrences are associated with poor treatment response. Timing of antiepileptic drugs withdrawal policies, however, have never been taken into account when investigating time to relapse following epilepsy surgery. *Methods*. Of the European paediatric epilepsy surgery cohort from the "TimeToStop" study, all 95 children with postoperative seizure recurrence following antiepileptic drug (AED) withdrawal were selected. We investigated how time intervals from surgery to AED withdrawal, as well as other previously suggested determinants of (timing of) seizure recurrence, related to time to relapse and to relapse treatability. Uni- and multivariable linear and logistic regression models were used. *Results*. Based on multivariable analysis, a shorter interval to AED reduction was the only independent predictor of a shorter time to relapse. Based on univariable analysis, incomplete resection of the epileptogenic zone related to a shorter time to recurrence. Timing of recurrence was not related to the chance of regaining seizure freedom after reinstallation of medical treatment. *Conclusion*. For children in whom AED reduction is initiated following epilepsy surgery, the time to relapse is largely influenced by the timing of AED withdrawal, rather than by disease or surgery-specific factors. We could not confirm a relationship between time to recurrence and treatment response. Timing of AED withdrawal should be taken into account when studying time to relapse following epilepsy surgery, as early withdrawal reveals more rapidly whether surgery had the intended curative effect, independently of the other factors involved.

Key words: epilepsy surgery, pediatric, childhood, seizure recurrence, antiepileptic drugs, antiepileptic drug withdrawal

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Epilepsy surgery is a highly successful treatment option for children with refractory focal structural epilepsy, with postoperative seizure freedom rates varying from 50-70% (Spencer and Huh, 2008). If antiepileptic drugs (AEDs) can be discontinued postoperatively and seizure freedom persists for many years, the child can be considered "cured" from epilepsy (Schmidt *et al.*, 2004). Seizure freedom rates, however, decline over the years after surgery (Spencer and Huh, 2008; Wiebe and Jette, 2012; Edelvik *et al.*, 2013), possibly related to underlying pathology (Bulacio *et al.*, 2012). The extent to which AED withdrawal contributes to the decrease of seizure freedom rates over time remains unknown. Overall predictors of postoperative seizure recurrences have been clearly identified in multivariable analyses and include specific pathology, incomplete resection of the anatomical lesion and epileptogenic zone, multifocal MRI abnormalities, preoperative generalised EEG abnormalities, prior surgery, multilobar resections, and epileptic abnormalities on postoperative EEG (Jeha *et al.*, 2007; Boshuisen *et al.*, 2012; Bulacio *et al.*, 2012; McIntosh *et al.*, 2012; Ladino *et al.*, 2014). Medical treatability of postoperative recurrences appears to differ between patients who had a recurrence following AED withdrawal and those who relapsed while still on drugs (Berg *et al.*, 2006; Kerling *et al.*, 2009).

It was recently suggested that there are two distinct types of seizure relapse; early recurrences (within 6 to 12 months) implicating a failure to define and resect the epileptogenic zone, and late recurrences that may arise after years, possibly reflecting the persistence or re-emergence of epileptogenic pathology (Najm *et al.*, 2013; Goellner *et al.*, 2013). Inherently, factors that have been associated with early recurrences included the need for invasive recordings, bilateral MRI abnormalities, and postoperative interictal EEG abnormalities (Jeha *et al.*, 2006; Jehi *et al.*, 2010; Najm *et al.*, 2013). Focal cortical dysplasia (FCD) type 1 and the absence of a clear pathological substrate in the resected tissue have been suggested to predict late recurrences (Jeha *et al.*, 2006; Najm *et al.*, 2013). Furthermore, it was reported that early recurrences are more likely to be AED-resistant compared to late relapses (Jeha *et al.*, 2007; Jehi *et al.*, 2010; Najm *et al.*, 2013; Goellner *et al.*, 2013).

We hypothesize that the time to postoperative seizure relapse is, to a large extent, also influenced by the timing of AED withdrawal, a factor that has, until now, not systematically been accounted for in the above studies. The suggestion put forward by Najm *et al.*, that timing of recurrence is largely determined by disease- and surgery-specific factors (Najm *et al.*, 2013), inspired us to investigate whether timing of AED withdrawal influences time to relapse, based on the data from the recently reported "TimeToStop" cohort (Boshuisen *et al.*, 2012). From this cohort of seizure-free children in whom AED withdrawal was initiated following epilepsy surgery, we identified those who relapsed during or after withdrawal and investigated the timing of recurrence, not only with regards to the predictors suggested by Najm *et al.*, (2013), but also with regards to the timing of AED withdrawal. This correlation has not been previously reported. Furthermore, we analysed whether time to relapse was associated with treatability of seizure recurrence.

Methods

We used the database of the TimeToStop study, a retrospective European multicentre cohort study that investigated how timing of AED withdrawal after epilepsy surgery related to seizure recurrence and eventual seizure freedom in a selected cohort of 766 children who started AED withdrawal after having reached postoperative seizure freedom. In this study, time to relapse had not yet been evaluated in relation to possible predictors (Boshuisen *et al.*, 2012).

For the specific purpose of the present study, we selected all patients with seizure recurrence during or after AED reduction (n=95). We investigated how the time of occurrence of the first relapse was related to: 1) the timing intervals from surgery to start and completion of AED withdrawal; 2) other determinants of postoperative seizure recurrence (Boshuisen *et al.*, 2012); and 3) previously suggested predictors of time to relapse (Najm *et al.*, 2013) (*table 1*). Furthermore, the time to relapse was related to its treatability, defined as regaining seizure freedom after restarting or change of medication. Definitions and classifications of the possibly predictive factors analysed here (*e.g.* type of surgery, aetiology, and completeness of resection) were identical to those described in the previous TimeToStop study. We defined "time to start of AED reduction" (TTR) as the interval from surgery to the first dose reduction of drugs, and "time to discontinuation of AEDs" (TTD) as the interval between surgery and complete cessation of drugs. Here, we defined "time at increased risk" as the interval between start of AED reduction and seizure relapse. To assess whether a reduction of drugs carried a relapse risk similar to that of complete AED discontinuation, we compared characteristics of children who relapsed during reduction with those who only had a recurrence after complete cessation of AEDs.

Statistical analysis

Uni- and multivariable linear regression analysis was used to correlate timing of seizure recurrence with

Table 1. Possible determinants of timing of seizure recurrence. Linear regression analysis of variables in relation to interval to seizure recurrence.

	Interval from surgery to recurrence			
	Univariable analysis		Multivariable analysis	
	p value	RC (95% CI)	*p* value	RC (95% CI)
Multifocal MRI lesions	0.95	0.35 (-11.34-12.04)		
Normal MRI	0.65	-9.90 (-52.73-32.92)		
Preoperative intracranial recordings performed	0.50	3.15 (-6.16-12.46)		
TTR (in months)	<0.001	0.96 (0.66-1.25)	0.05	0.90 (0.02-1.79)
TTD (in months)	0.02	0.77 (0.15-1.38)	0.64*	-0.68 (-4.84-3.48)*
Incomplete resection of anatomical lesion	0.57	-2.89 (-12.89-7.12)		
Incomplete resection of epileptogenic zone	0.02	-25.19 (-46.29–4.09)	0.10	-17.1 (-38.0-3.85)
Type of Surgery				
Lobar resection (reference)	-	-		
Hemispherectomy	0.06	-12.46 (-25.57-0.64)	0.09	-9.47 (-20.6-1.61)
Multilobar resection	0.37	-5.96 (-19.06-7.15)	0.87	-0.92 (-12.1-10.2)
Postoperative EEG findings				
No epileptic discharges (reference)	-	-		
Epileptic discharges	0.69	1.96 (-7.63-11.55)		
No postoperative EEG performed	0.27	-8.89 (-24.94-7.16)		
Aetiology				
MCD (reference)	-	-		
Tumour	0.74	1.74 (-8.71-12.18)		
Vascular lesions	0.25	-9.57 (-25.81-6.67)		
HS	0.95	-0.42 (-13.62-12.79)		
Other aetiologies	0.99	0.20 (-31.09-31.50)		

RC: regression coefficient, indicating the change in interval to seizure recurrence (in months) with every unit or category change in the predictor; CI: confidence interval; MCD: malformations of cortical development; HS: hippocampal sclerosis; TTR: mean interval to start of reduction of AEDs; TTD: mean interval to complete cessation of AEDs.
*Separate models were used for TTR and TTD because these were highly correlated.

possible determinants. Determinants with *p* values <0.1 were used in a multivariable model. Logistic regression was used to study how time intervals between surgery and relapse related to treatability. To identify possible differences between children who relapsed during reduction with those who only had a recurrence after complete cessation of AEDs, χ^2 tests and independent t-tests were used where appropriate.

Results

Timing of recurrences

The median time from surgery to seizure recurrence was 25.3 months; 14% of the 95 patients had a relapse within 6 months, 24% within 12 months, and 48% within 24 months, cumulatively (*figure 1*). Median interval to start of reduction of AEDs (TTR) was 11.9±12.3 months.

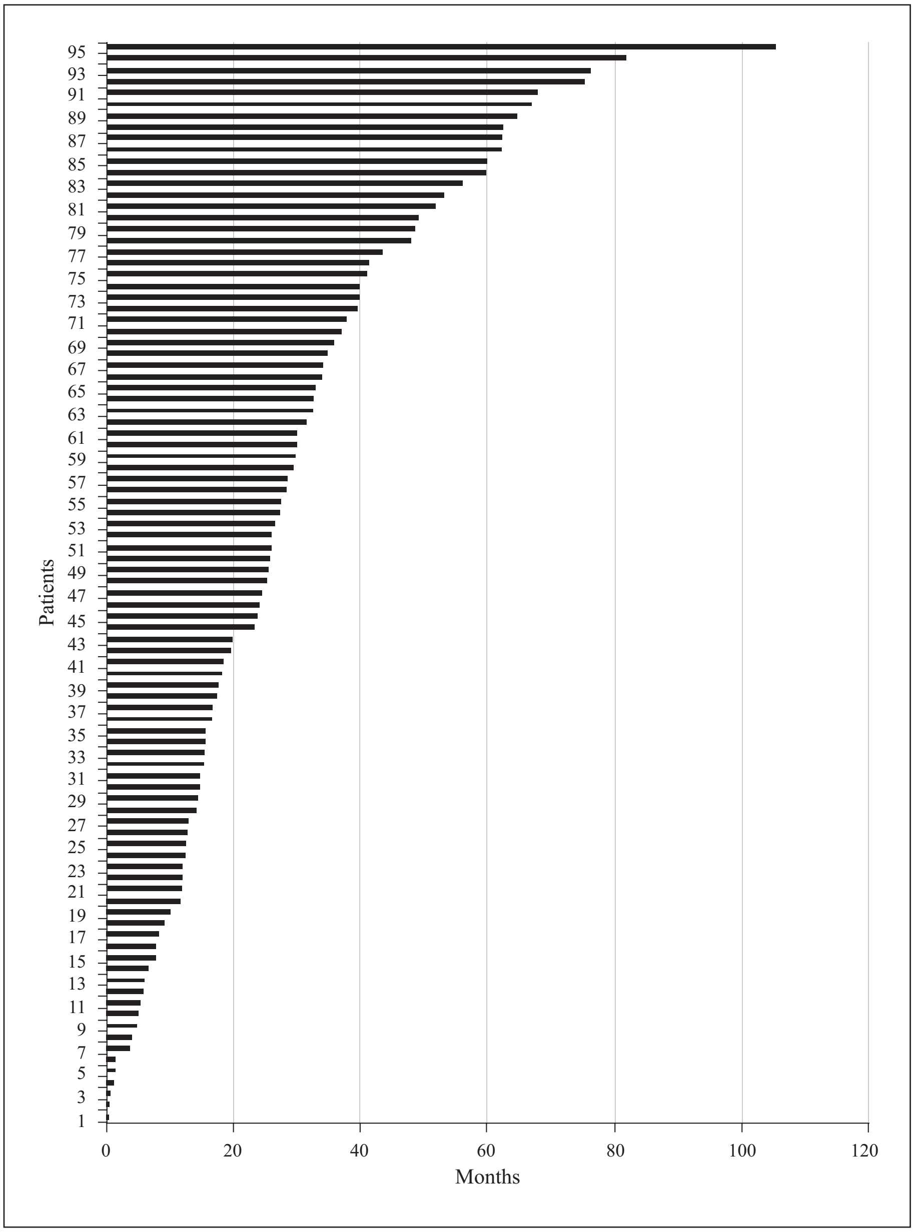

Figure 1. Interval between surgery and relapse.
Intervals from surgery to seizure recurrences in months, for all included patients (*n*=95).

The median “time at increased risk”, defined as the interval from the beginning of AED reduction to recurrence, was 8.7 months, with 44% of relapses occurring within 6 months after the start of withdrawal, 56% within 12 months, and 81% within 24 months. Median interval to complete discontinuation of AEDs (TTD) in children who achieved complete AED discontinuation (*n*=36) was 21.2±12.5 months. In this subgroup, the median interval after complete discontinuation of AEDs until seizures recurred was 10.8 months, with 46% of children relapsing within 6 months, 51% within 12 months, and 70% within 24 months after complete withdrawal. As illustrated in *figure 1*, we found no specific dichotomy with regards to the time to relapse in this cohort. Recurrences occurred both early and late after surgery, with a wide range of intervals.

Determinants of the time to relapse

We first analysed how the previously identified determinants of seizure recurrences (Boshuisen *et al*., 2012), and of timing of seizure relapse (Najm *et al*., 2013), related to time to relapse. Using univariable analysis, incomplete resection of the epileptogenic zone significantly correlated with a shorter time to relapse, and hemispherectomy tended to be associated with shorter intervals to recurrence. The two factors that were related to a longer time to relapse were a longer interval to start of medication withdrawal (TTR) and later complete discontinuation of medication (TTD). Using multivariable analysis, the only determinant that remained significantly associated with a longer time to relapse was a longer interval to start of AED reduction (*table 1*). When children who relapsed after initiation of AED reduction were compared with those who had a recurrence only after AEDs had completely been discontinued, no significant differences in epilepsy- or surgery-related outcome predictors were identified (data not shown).

Treatability of recurrences

Time to relapse was not related to the chance of regaining seizure freedom after reinstallation of medical treatment (OR: 1.00; 95% CI: 0.98-1.02; p=0.83). The time corresponding to being at "increased risk", after initiation or completion of AED withdrawal, until seizures recurred, was not related to treatability of seizure recurrences (OR: 1.01; 95% CI: 0.98-1.04; p=0.65 and OR: 1.02; 95% CI: 0.98-1.06; p=0.41, respectively).

Discussion

In 95 children with a postoperative seizure recurrence among a retrospective European cohort of 766 children who had started AED withdrawal after epilepsy surgery (Boshuisen *et al.*, 2012), timing of AED withdrawal was the only independent predictor of the time to relapse. Timing of seizure recurrence was not associated with subsequent medication intractability. These findings add to our understanding of the relationship between postoperative drug policies and seizure outcome. Having previously established that earlier withdrawal does not affect eventual seizure outcome (Boshuisen *et al.*, 2012), we now demonstrate that timing of AED withdrawal is closely related to the timing of relapse, providing further evidence that early withdrawal uncovers sooner whether or not surgery had the intended curative effect.

Based on a series of previous studies that included children and adults, Najm *et al.* (2013) recently proposed, in a highly original review, that the timing of seizure relapse implicates a difference in underlying pathophysiological mechanisms. In their studies, factors that were associated with an inability to accurately define or completely resect the epileptogenic zone predicted early recurrence, whereas late recurrences were suggested to reflect ongoing epileptogenicity. In adults who underwent anterior temporal lobectomy, a high preoperative seizure frequency and generalised tonic-clonic seizures, bilateral MRI abnormalities, spikes on a six-month postoperative EEG, and the need for invasive EEG diagnostics significantly related to early recurrences (Jeha *et al.*, 2006). After tailored temporal resection in adults, early recurrence within six months was a significant predictor of a non-contiguous, distant focus (Jehi *et al.*, 2010). Furthermore, of the patients who relapsed after a temporal resection (Jehi *et al.*, 2010; Goellner *et al.*, 2013), as well as adults or children who underwent a frontal resection (Jeha *et al.*, 2007), those with early postoperative recurrences were more likely to become intractable to AED treatment than those who had a late seizure relapse.

Based on the current retrospective study of children who relapsed after surgery, a tendency toward earlier recurrences tended to correlate with an inability to accurately define or completely resect the epileptogenic zone, however, we could not prove statistical independence. In addition, we did not find a relationship between time to relapse and reaction to subsequent treatment. Several explanations can account for the different findings between those reported in previous studies and those reported here. First, in earlier studies, timing of AED withdrawal was not systematically accounted for when relating different variables with the time of first seizure relapse (Jeha *et al.*, 2006; Jehi *et al.*, 2010; Goellner *et al.*, 2013), whereas it was the only independent predictor in our analysis. Many of the previously suggested predictors of timing of seizure recurrence (Najm *et al.*, 2013) have recently been shown to also influence the decision to start AED reduction (Boshuisen *et al.*, 2012), and may therefore have confounded the alleged relationship between bilateral MRI abnormalities, EEG findings, the need for invasive diagnostics, (lack of) specific pathology, and the timing of relapse and its treatability. Nevertheless, if these clinical factors had indeed delayed the decision to withdraw AEDs (Boshuisen *et al.*, 2012), it is even more striking that the Cleveland study predicted earlier relapse (Jeha *et al.*, 2006; Jehi *et al.*, 2010; Najm *et al.*, 2013). This underlines the need for multivariable analyses including all possible determinants of time to relapse in future studies, including drug withdrawal.

Second, in most studies referred to by Najm and coworkers (Jeha *et al.*, 2006; Jehi *et al.*, 2010; Najm *et al.*, 2013), only adult patients were included. Underlying pathology, presurgical diagnostics, surgical strategies, and AED policies may have differed between adults and children.

Third, we acknowledge that the TimeToStop cohort is a selected sample of only seizure-free children who started postoperative AED withdrawal, in contrast to the total population of surgical cohorts previously investigated (Jeha *et al.*, 2006; Jeha *et al.*, 2007; Jehi *et al.*, 2010). Factors that determine time to relapse in patients who continue drugs may differ from those who withdraw medication. Children with unprovoked postoperative seizure recurrences, while still on AEDs, were not included in the current analysis, and the influence of clinical factors that specifically predict early relapse, as listed above, may thus have been difficult to detect.

The strong association between timing of AED reduction and timing of seizure relapse in this study provides further evidence that AED withdrawal unmasks incomplete surgical success and that AEDs merely act to symptomatically suppress seizures (Loscher and Schmidt, 2011). Based on the univariable analysis, we could confirm the previously proposed correlation between incomplete resection of the epileptogenic zone and shorter time to recurrence (Jehi *et al.*, 2010; Najm *et al.*, 2013). Nevertheless, even after the presumed complete resection of the epilepsy-causing pathology, patients may carry a risk of relapse following AED withdrawal, since only part of a potentially larger epileptogenic network may have been removed (Jehi *et al.*, 2010; Wiebe and Jette, 2012; Najm *et al.*, 2013). Perhaps *de novo* resistance of seizures after surgery partly reflects the natural history of the primary underlying epilepsy, which cannot always be cured by focussing on a single target since most epilepsies develop from complex alterations resulting in an epileptic network in the brain (Bertram *et al.*, 1998; Engel *et al.*, 2013).

Conclusion

For children in whom AED reduction is initiated following epilepsy surgery, the time to relapse is influenced more by AED withdrawal policies than by disease- or surgery-specific factors. Although our findings stem from a highly selected cohort, they suggest that studies into occurrence and timing of postoperative seizure relapse need to take AED withdrawal policies into account. Previous suggestions of a relationship between time to recurrence and treatability could not be confirmed. □

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References

Berg AT, Vickrey BG, Langfitt JT, *et al*. Reduction of AEDs in postsurgical patients who attain remission. *Epilepsia* 2006; 47: 64-71.

Bertram EH, Zhang DX, Mangan P, Fountain N, Rempe D. Functional anatomy of limbic epilepsy: a proposal for central synchronization of a diffusely hyperexcitable network. *Epilepsy Res* 1998; 32: 194-205.

Boshuisen K, Arzimanoglou A, Cross JH, *et al*. Timing of antiepileptic drug withdrawal and long-term seizure outcome after paediatric epilepsy surgery (TimeToStop): a retrospective observational study. *Lancet Neurol* 2012; 11: 784-91.

Bulacio JC, Jehi L, Wong C, *et al*. Long-term seizure outcome after resective surgery in patients evaluated with intracranial electrodes. *Epilepsia* 2012; 53: 1722-30.

Edelvik A, Rydenhag B, Olsson I, *et al*. Long-term outcomes of epilepsy surgery in Sweden: a national prospective and longitudinal study. *Neurology* 2013; 81: 1244-51.

Engel Jr. J, Thompson PM, Stern JM, Staba RJ, Bragin A, Mody I. Connectomics and epilepsy. *Curr Opin Neurol* 2013; 26: 186-94.

Goellner E, Bianchin MM, Burneo JG, Parrent AG, Steven DA. Timing of early and late recurrence after temporal lobe epilepsy surgery. *Epilepsia* 2013; 54: 1933-41.

Jeha LE, Najm I, Bingaman W, Dinner D, Widdess-Walsh P, Luders H. Surgical outcome and prognostic factors of frontal lobe epilepsy surgery. *Brain* 2007; 130(Pt 2): 574-84.

Jeha LE, Najm IM, Bingaman WE, *et al*. Predictors of outcome after temporal lobectomy for the treatment of intractable epilepsy. *Neurology* 2006; 66: 1938-40.

Jehi LE, Silveira DC, Bingaman W, Najm I. Temporal lobe epilepsy surgery failures: predictors of seizure recurrence, yield of reevaluation, and outcome following reoperation. *J Neurosurg* 2010; 113: 1186-94.

Kerling F, Pauli E, Lorber B, Blumcke I, Buchfelder M, Stefan H. Drug withdrawal after successful epilepsy surgery: how safe is it? *Epilepsy Behav* 2009; 15: 476-80.

Ladino LD, Hernández-Ronquillo L, Téllez-Zenteno JF. Management of antiepileptic drugs following epilepsy surgery: a meta-analysis. *Epilepsy Res* 2014; 108: 765-74.

Loscher W, Schmidt D. Modern antiepileptic drug development has failed to deliver: ways out of the current dilemma. *Epilepsia* 2011; 52: 657-78.

McIntosh AM, Averill CA, Kalnins RM, *et al*. Long-term seizure outcome and risk factors for recurrence after extratemporal epilepsy surgery. *Epilepsia* 2012; 53: 970-8.

Najm I, Jehi L, Palmini A, Gonzalez-Martinez J, Paglioli E, Bingaman W. Temporal patterns and mechanisms of epilepsy surgery failure. *Epilepsia* 2013; 54: 772-82.

Schmidt D, Baumgartner C, Loscher W. The chance of cure following surgery for drug-resistant temporal lobe epilepsy. What do we know and do we need to revise our expectations? *Epilepsy Res* 2004; 60: 187-201.

Spencer S, Huh L. Outcomes of epilepsy surgery in adults and children. *Lancet Neurol* 2008; 7: 525-37.

Wiebe S, Jette N. Pharmacoresistance and the role of surgery in difficult to treat epilepsy. *Nat Rev Neurol* 2012; 8: 669-77.

TEST YOURSELF

Q1. When parents ask you whether it is safe to withdraw AEDs in their child who became seizure-free after anticipated curative epilepsy surgery, how would you inform them on risks and benefits?
Q2. Does postoperative AED withdrawal influence the "natural course" of the epilepsy?
Q3. Is early postoperative withdrawal of AEDs unsafe in children?
Note:
Answers are based on two review papers (Braun & Schmidt, Curr Opin Neurol 2014;27:219-226; Ladino et al. Epil Res 2014;108:765-774), and on two research papers (Boshuisen et al. Lancet Neurol 2012;11:784-791, Boshuisen et al. Epileptic Disord 2014; 16: 305-11).

You can check for the correct answer by visiting the Educational Centre section of www.epilepticdisorders.com