



Interpreting Seizure Counts After Temporal Lobectomy: Not Just One-Two-Three

Latency to first seizure after temporal lobectomy predicts long-term outcome.

Buckingham SE, Chervoneva I, Sharan A, Zangaladze A, Mintzer S, Skidmore C, Nei M, Evans J, Pequignot E, Sperling MR. *Epilepsia* 2010;51(10):1987–1993.

PURPOSE: Temporal lobectomy is a well-established treatment for refractory temporal lobe epilepsy, yet many patients experience at least one seizure postoperatively. Little is known about the prognostic significance of the time from surgery to first seizure relapse in predicting long-term outcome. **METHODS:** In a retrospective analysis of patients who reported at least one complex partial seizure (CPS) or generalized tonic-clonic seizure (GTCS) after anterior temporal lobectomy ($n = 268$), we used a nominal response logistic model to predict the odds ratio (OR) of a seizure outcome based on length of the latency period from surgery to first postoperative seizure. A modified Engel outcome class scheme was used. We controlled for factors known to influence postoperative outcome, including history of tonic-clonic seizures, intelligence quotient (IQ), preoperative seizure frequency, magnetic resonance imaging (MRI) findings, and history of febrile convulsions. **RESULTS:** In the univariate analysis, the latency from surgery to the first postoperative disabling seizure was significantly associated with long-term outcome. Longer latency was associated with higher odds of being seizure-free or improved (modified Engel's classes 1, 2, and 3) relative to the unimproved state (class 4) ($p < 0.001$, 0.001 and 0.004, respectively). Conversely, a shorter latency increased the likelihood of achieving the worst prognosis (class 4) relative to class 1 ($p < 0.001$). Multivariate analysis yielded similar results. **DISCUSSION:** Latency to the first postoperative seizure predicts long-term outcome, with short latencies portending poor prognosis and long latencies portending a good prognosis. This information can be used for patient counseling and may influence decisions regarding reoperation.

When is a postoperative seizure equivalent to "epilepsy recurrence" after epilepsy surgery?

Jehi L, Sarkis R, Bingham W, Kotagal P, Najm I. *Epilepsia* 2010;51(6):994–1003.

PURPOSE: Up to one-half of epilepsy surgery patients will have at least one seizure after surgery. We aim to characterize the prognosis following a first postoperative seizure, and provide criteria allowing early identification of recurrent refractory epilepsy. **METHODS:** Analyzing 915 epilepsy surgery patients operated on between 1990 and 2007, we studied 276 who had $\neq 1$ seizure beyond the immediate postoperative period. The probability of subsequent seizures was calculated using survival analysis. Patients were divided into seizure-free (no seizures for $\neq 1$ year) and refractory (persistent seizures) and analyzed using multivariate regression analysis. **RESULTS:** After a first seizure, 50% had a recurrence within 1 month and 77% within a year before the risk slowed down to additional 2–3% increments every two subsequent years. After a second seizure, 50% had a recurrence within 2 weeks, 78% within 2 months, and 83% within 6 months. Having both the first and second seizures within six postoperative months [odds ratio (OR) 4.04; 95% confidence interval (CI) 2.05–8.40; $p = 0.0001$], an unprovoked initial recurrence (OR 3.92; 95% CI 2.13–7.30; $p < 0.0001$), and ipsilateral spikes on a 6-months postoperative electroencephalography (EEG) (OR 2.05; 95% CI 1.10–3.88; $p = 0.025$) predicted a poorer outcome, with 95% of patients who had all three risk factors becoming refractory. All patients with cryptogenic epilepsy and recurrent seizures developed refractoriness. **DISCUSSION:** Seizures will recur in most patients who present with their first postoperative event, with one-third eventually regaining seizure-freedom. Etiology and early and unprovoked postoperative seizures with epileptiform activity on EEG at six postoperative months may predict recurrent medical refractoriness.



Commentary

Although near-complete seizure control correlates well with quality of life improvement after temporal lobectomy, several factors may influence these data and their interpretation. Among patients with at least one postoperative seizure, the studies discussed herein sought to forecast long-term seizure control by two methods: 1) latency to first seizure, and 2) number of postoperative seizures.

The Buckingham et al. study found that longer latency to first postoperative seizure gave higher odds of being seizure-free (SF) or improved. Such “survival analysis” (i.e. the proportion of patients reaching an outcome of interest over time) accounts for staggered patient recruitment, variation in length of follow-up, and a wide range of seizure frequencies (1); therefore it is quite applicable for studies of this type. For ethical considerations, these studies must be performed as practiced; thus 90% of the subjects in the studies by Buckingham et al. took anti-epileptic drugs (AEDs), likely producing a significant range of drug quantity. Moreover, readers must realize the several reporting biases inherent in these evaluations. Surrogate masked seizure measuring methods, not employed in these two studies, can minimize such biases (1).

Epilepsy seizure precipitants always need to be considered, but particularly when relapse occurs following an extended SF period. Thus, Jehi et al. found that an unprovoked initial postoperative seizure was four times more likely to herald refractory seizures than a provoked initial attack. This finding suggests that a brain requiring an identifiable precipitant to launch a seizure has a higher inherent seizure threshold than one producing apparently spontaneous attacks. Most seizure surgery follow-up studies do not include identifiable and measurable precipitants such as stress, sleep-loss, fever, and alcohol-withdrawal (2). These data suggest that postsurgical outcome in terms of seizure control may be significantly influenced by lifestyle. Factors underlying seizure recurrence must be sought.

Protocols of both these studies defined terminal remission as 1 year SF; whereas Engel’s classification of postoperative outcome requires the more substantial 2-year period for assignment to his classes I, II, and III (3).

While the Buckingham et al. study relates only to temporal lobectomy, that of Jehi et al. sought criteria for early identification of postoperative refractory seizures by following *all* epilepsy surgery patients who had at least one seizure beyond the immediate postoperative period. This method assumes that sufficiently common features apply to any procedure in any lobe for any pathogenesis. A more prompt recurrence after a second postoperative seizure and a worse outlook if seizures were apparently unprovoked likely reflect the lingering lower threshold mentioned above. However, the increasing proportion of patients with persistent seizures after each postoperative seizure (Figure 2 in Jehi et al.) raises the possibility that each postoperative attack helps lower the threshold, nullifying any surgically induced improvement. Seizures may significantly increase pro-inflammatory cytokines including interleukin (IL)-1B and IL-6. IL-1B increases glutamatergic neurotransmission and seizures by increasing calcium influx induced by NMDA stimulation, inhibiting glutamate uptake by astrocytes, and decreasing GABA currents

(4). These effects can create a “seizures beget seizures” effect, which may underlie the clinically common clustering of ictal events.

Curiously omitted from the Jehi et al. abstract is the substantial influence of pathologically verified etiology on outcome, ranging from 29% SF with malformations of cortical development (MCD) to 88% SF with vascular etiologies. The degree of epilepsy multifocality implied by an etiology may be one of several factors; for example, EEG evidence of this as multifocal spikes appeared in 70% of MCD patients despite sufficient congruence of ictal EEG and imaging to warrant resective surgery (5).

For the clinician discussing the feasibility of resective surgery with a patient, risks need to be balanced against potential benefit. For example, about 20 percent to 50 percent of patients undergoing temporal lobectomy suffer a decline in verbal memory (6, 7), and about 20% have persistent visual field deficits >90 degrees, sufficient to disqualify them from driving in some jurisdictions (8). Additionally, about one patient in eight will have permanent psychiatric condition (9). These data indicate that postoperative seizure counts should be presented separately for patients *without* any permanent deficit. Most studies, including these, do not include this aspect.

Finally, as can be gleaned from the foregoing, future publications should comprise the following: 1) data obtained by surrogate interviewers, 2) a 2-year duration for SF status, and 3) number of patients that are worse.

by Warren T. Blume, M.D.

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