Predicting a Storm by Watching the Waves

Time-Dependent Risk of Seizures in Critically Ill Patients on Continuous Electroencephalogram.

Struck AF, Osman G, Rampal N, Biswal S, Legros B, Hirsch LJ, Westover MB, Gaspard N. *Ann Neurol* 2017;82:177–185.

OBJECTIVE: Find the optimal continuous electroencephalographic (CEEG) monitoring duration for seizure detection in critically ill patients. METHODS: We analyzed prospective data from 665 consecutive CEEGs, including clinical factors and time-to-event emergence of electroencephalographic (EEG) findings over 72 hours. Clinical factors were selected using logistic regression. EEG risk factors were selected a priori. Clinical factors were used for baseline (pre-EEG) risk. EEG findings were used for the creation of a multistate survival model with 3 states (entry, EEG risk, and seizure). EEG risk state is defined by emergence of epileptiform patterns. RESULTS: The clinical variables of greatest predictive value were coma (31% had seizures; odds ratio [OR] = 1.8, $p < 0.01$) and history of seizures, either remotely or related to acute illness (34% had seizures; OR = 3.0, $p < 0.001$). If there were no epileptiform findings on EEG, the risk of seizures within 72 hours was between 9% (no clinical risk factors) and 36% (coma and history of seizures). If epileptiform findings developed, the seizure incidence was between 18% (no clinical risk factors) and 64% (coma and history of seizures). In the absence of epileptiform EEG abnormalities, the duration of monitoring needed for seizure risk of <5% was between 0.4 hours (for patients who are not comatose and had no prior seizure) and 16.4 hours (comatose and prior seizure). INTERPRETATION: The initial risk of seizures on CEEG is dependent on history of prior seizures and presence of coma. The risk of developing seizures on CEEG decays to <5% by 24 hours if no epileptiform EEG abnormalities emerge, independent of initial clinical risk factors.

Commentary

It is midnight. The waves dance across the screen in the darkened room.

It is decision time for the weary neurologist: Go to bed and hope for no seizures before morning, stay up a while longer, or take a nap and set the alarm for 3 am? We have all had the unfortunate experience of going to bed thinking things are stable, only to review the overnight EEG the next morning to find a seizure at 4 am. A nightly dilemma in many hospitals, but Struck and colleagues have come to the rescue. They have provided a useful set of clinical and EEG factors to help predict the likelihood of seizures during the ensuing 72 hours. However, it is only a partial rescue—too many factors remain unknown, and it will be awhile before the aforementioned neurologist can sleep easily.

The primary goal of this study was to assess the likelihood of a seizure during a continuous EEG-videomonitoring study in an intensive care setting based on three factors: 1) presence of coma, 2) history of seizures, and 3) presence of interictal epileptiform features on the EEG. Both the value of the study and its weakness are related to the simplicity of these factors. It was necessary for clarity and adequate statistical power to make each of these variables simple dichotomies: *coma* was defined as inability to make a "meaningful response" to stimuli, *history of seizures* could mean 20 years ago or 2 minutes ago, and the EEG features designated as *epileptiform* are heterogenous (sporadic epileptiform discharges, lateralized periodic discharges [LPDs], lateralized rhythmic delta activity [LRDA], brief ictal rhythmic discharges, bilateral independent periodic discharges [BRDs], and lateralized spike-waves).

The authors collected data prospectively on 665 continuous EEGs and related the presence or absence of these three factors to the occurrence of a seizure later in the recording. The duration of all EEGs analyzed was at least 24 hours but no more than 72 hours, because bias can arise from the tendency of clinicians to run short EEGs for patients considered low-risk and longer one for patients considered high risk. Thus, the endpoint for each patient was either discontinuation of the record within this time window or the occurrence of the first seizure. Clinical state was assessed before the EEG, then risk was assessed by calculation of three possible transitions: from entry (nothing has happened yet) to risk state (epileptiform EEG pattern), and from risk state to seizure (electrographic or clinical), or directly from entry state to seizure state. Disconcertingly, 41% of seizures followed this last pattern; that is, no EEG "warning" before a seizure.

Twenty-three percent of these patients had a seizure, including 34% of those in coma and 31% of those with a history of seizure. This validates many previous studies documenting

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the value of continuous EEG in the intensive care unit. Struck et al. found that the EEG pattern before the seizure did have predictive value but was most useful among those with one of the two clinical risk factors: Only 18% of noncomatose patients with no history of seizures had a seizure, even with interictal epileptiform features, whereas 64% of those comatose with a prior seizure history and interictal epileptiform features had a seizure.

These data help our late-night neurologist only so much. The first problem is the definition of *epileptiform*. It is a bit circular to label some EEG patterns epileptiform a priori. For example, is LRDA epileptiform? Rodriguez et al. (1) found it to be associated with seizures to a relatively weak degree, but so are lateralized lesions on MRI. Is this pattern more predictive of seizures than focal polymorphic delta? Some of the patterns that the authors consider epileptiform were really too uncommon in this population to state their predictive value; for example, lateralized spike-waves or BRDs. Generalized rhythmic delta activity was included in a table labeled "EEG risk factors for electrographic seizures" but apparently was not considered in the state transition analysis—it was not associated with seizures, as concluded from other studies (1). Some findings from Struck and colleagues make sense within this time horizon but not in a longer view. For example, focal sporadic epileptiform discharges (e.g., spikes) are most definitely associated with seizures, as every EEGer since Berger has believed. But in this population, although commonly seen, they were not predictive of seizures for the subsequent 72 hours. As the authors note, we need more data about the predictive value of individual patterns.

Another factor that could not be quantified from this study (although it can be inferred from survival curves) was the temporal evolution of the patterns. Consider an analogy: An islander stands on the seashore, watching the ocean waves. One especially big wave may not mean much, but if they become higher and higher over a period of hours, she may conclude that a hurricane is likely. If a sporadic EEG spike is becoming more frequent, and especially if it is becoming periodic, that seems likewise ominous. As we watch a continuous EEG, we note whether periodic waves are becoming more frequent, higher in amplitude, and sharper. I think of these as crescendo paroxysmal discharges. In this situation, some of us will advise stronger drug treatment. We will certainly sleep less well. There is also a sort of decrescendo pattern one may see with time or proper treatment. In that situation, LPDs might be less worrisome—they may represent improvement, not deterioration (2). That sequence was not evaluated in the study by Struck et al.

A valuable feature of this paper is the calculation of how long a continuous EEG should be to reduce the risk of "missing" a seizure over the next 72 hours to less than 5%. With no clinical risk factors and a non-epileptiform EEG, 24 minutes is fine. This is because the survival curves from this study convincingly demonstrate that the risks of transitioning states—entry to EEG risk, or EEG risk to seizure—drop off very rapidly with time. This is reassuring. Forty-eight hours is apparently enough for high-risk patients; also reassuring, although perhaps the clock resets if the EEG worsens or if seizures actually occur.

Finally, there is the assumption that preventing or stopping seizures is clinically beneficial to patients. We tend to hold this truth to be self-evident; of course, it needs to be validated for specific pathologies and seizure types.

The results of this study are valuable because they allow us to begin putting numbers to our guesses (there is a 20% chance of rain tomorrow; there is a 20% chance of a seizure tomorrow). What is the acceptable level of risk for carrying an umbrella? For missing a seizure? Acceptable risk involves multiple value decisions (3). Those who think a human can, or should, watch ten EEG monitor screens continuously for several hours and never miss anything are not being realistic, and computerized alerts are still too unreliable. Those are questions that remain in the realm of physician judgment. Go to bed? You're the doctor, you decide.

by Edward Faught, MD

References

1. Rodriguez Ruiz A, Vlachy J, Lee JW, Gilmore EJ, Ayer T, Haider HA, Gaspard N, Ehrenberg JA, Tolchin B, Fantaneanu TA, Fernandez A, Hirsch LJ, LaRoche S; Critical Care EEG Research Consortium. Association of periodic and rhythmic EEG patterns with seizures in critically ill patients. *JAMA Neurology* 2017;74:182–188.
2. Brenner RP, Schaul N. Is it status? *J Clin Neurophysiol* 2002;43(suppl 3):103–113.
3. Fischhoff B, Lichtenstein S, Slovic P, Derby SL, Keeney R. *Acceptable Risk*. New York: Cambridge University Press, 1981.