


# Electroencephalographic Seizure or Electroencephalographic Status Epilepticus in the ICU? Is it Time to Focus Just on Electroencephalographic Status Epilepticus?

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## Electrographic Seizures and Outcome in Critically Ill Children [published online ahead of print, 2021 Apr 23]

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**Objective:** To determine the association between electroencephalographic seizure (ES) and electroencephalographic status epilepticus (ESE) exposure and unfavorable neurobehavioral outcomes in critically ill children with acute encephalopathy. **Methods:** This was a prospective cohort study of acutely encephalopathic critically ill children undergoing CEEG. ES exposure was assessed as<sup>1</sup> no ES/ESE,<sup>2</sup> ES, or<sup>3</sup> ESE. Outcomes assessed at discharge included the Glasgow Outcome Scale-Extended Pediatric version (GOS-E-Peds), Pediatric Cerebral Performance Category (PCPC), and mortality. Unfavorable outcome was defined as a reduction in GOS-E-Peds or PCPC score from pre-admission to discharge. Stepwise selection was used to generate multivariate logistic regression models that assessed associations between ES exposure and outcomes while adjusting for multiple other variables. **Results:** Among 719 consecutive critically ill subjects, there was no evidence of ES in 535 subjects (74.4%), ES in 140 subjects (19.5%), and ESE in 44 subjects (6.1%). The final multivariable logistic regression analyses included ES exposure, age dichotomized at 1 year, acute encephalopathy category, initial EEG background category, comatose at CEEG initiation, and the Pediatric Index of Mortality 2 score. There was an association between ESE and unfavorable GOS-E-Peds (odds ratio 2.21, 95% CI: 1.07-4.54) and PCPC (odds ratio 2.17, 95% CI: 1.05-4.51) but not mortality. There was no association between ES and unfavorable outcome or mortality. **Conclusions:** Among acutely encephalopathic critically ill children, there was an association between ESE and unfavorable neurobehavioral outcomes, but no association between ESE and mortality. ES exposure was not associated with unfavorable neurobehavioral outcomes or mortality.

## Commentary

Over the last decade, the number of patients undergoing continuous EEG monitoring (CEEG) in the pediatric intensive care unit (PICU) has consistently increased.<sup>1</sup> One of the goals of CEEG is to monitor for electrographic seizures (ES) and electrographic status epilepticus (ESE).<sup>2</sup> Most physicians aim to completely eliminate all seizures and ESE.<sup>3</sup>

As a practicing epileptologist at an academic center, I can identify with the responsibility to detect every subclinical seizure so that it can be appropriately treated. Now let us consider an intubated, comatose patient who is critically ill with febrile infection-related epilepsy syndrome, on a pentobarbital drip while also on a combination of 3 antiseizure medications (ASM) with an overall suppressed EEG background. Let us assume that despite medication, this patient continues to have 3 electrographic seizures every hour—each lasting 60 seconds. This begs the question: Are these seizures an epiphenomenon or will they independently affect outcome if left untreated? In the above situation, I have asked myself whether the benefit of aggressively treating every electrographic seizure outweighs the potential adverse effects from incremental ASM. Previous publications suggest that such adverse events occur in up to 20% patients and are usually serious.<sup>4</sup>

Topjian et al.<sup>5</sup> studied 200 patients and Payne et al.<sup>6</sup> studied 259 patients showing that ESE was associated with higher mortality than ES by the time of discharge from the PICU. Both studies looked at mortality and Pediatric Cerebral Performance Category (PCPC) scores as outcome measures. Topjian's study categorized ES as either present or absent while Payne analyzed ES as a continuous variable and found that above a critical threshold of 12 minutes of electrographic seizures per hour (20%); outcomes were dramatically worse. Wagenman et al.<sup>7</sup> recruited 137 patients and reported outcomes on 60 previously normal children several months after discharge (median 2.7 years), again showing worse outcomes (unfavorable Glasgow outcome scores-Extended Pediatric version and lower Pediatric Quality of Life inventory scores) after ESE.

Overall, the question of “admissible seizures” (ES that could be left untreated) is difficult to study without addressing the following relevant questions: Are ES just biomarkers of brain injury or independent predictors of outcome? Is there a threshold beyond which ES is likely to become ESE and therefore change outcome? What is the best tool and best time to assess these outcomes? How much of the outcome is dependent on the etiology of the encephalopathy? How does one adjust for





clinical variables, EEG variables, and variable outcome measures (mortality vs functional outcomes)?

In the recent article published in neurology, Fung et al.<sup>8</sup> have tried to address most of the above questions. The authors included all 719 consecutive patients admitted to the PICU for CEEG monitoring over a time span of 2 years. Neonates, patients who had undergone resective epilepsy surgery, and patients who had received care for more than 2 days for refractory status epilepticus elsewhere were excluded. The authors looked at the association between ES and ESE and unfavorable outcomes at the time of discharge from the PICU. Unfavorable outcomes were defined as a decrease of one or more points from baseline Glasgow Outcome Scale-Extended Pediatric version (GOS-E-P), PCPC, or mortality. Pediatric Index of Mortality 2 (PIM2) and Pediatric Risk of Mortality III (PRISM3) were scored as one of the clinical variables. Patients underwent a median of 23 hours of CEEG as guided by a uniform institutional guideline based on published consensus statements.<sup>2</sup> ESE was defined in this study as a single seizure lasting longer than 30 minutes or repeated seizures that occupied  $\geq 30$  minutes out of an hour-long epoch. ES was categorized as present or absent.

#### **How well does this study address our questions above?**

For simplicity, let us categorize these questions into two main groups

#### **I: Can we separate ES/ESE as independent factors associated with outcomes?** The short answer is yes.

The authors used several clinical and EEG variables that could serve as surrogate markers for brain injury including presence of ES/ESE, etiology of encephalopathy as structural or nonstructural, clinical history of epilepsy, presence of coma at EEG initiation, and EEG background (5 categories were studied ranging from normal to attenuated and featureless). They methodically identified variables found to be clinically significant on univariate analysis and then analyzed covariates and finally used all variables in the multivariable logistic regression to test association of ES/ESE with unfavorable outcomes on GOS-E-P and PCPC scores (thus accounting for all other confounders). ESE was associated with unfavorable GOS-E-P (odds ratio 2.21; 95% CI: 1.07-4.54) and PCPC (odds ratio 2.17, 95% CI: 1.05-4.54) but not mortality while ES was not associated with any unfavorable outcomes.

#### **II. Does ESE predict unfavorable outcomes independent of underlying illness?** The answer is yes

The authors performed an analysis assessing 4 subgroups: 339 previously neurobehaviorally normal children, 506 patients with acute structural or non-structural encephalopathy, 608 patients without prior epileptic encephalopathy, and 611 patients with mental status worse than baseline, and once again found the results to be similar to the primary analysis which was that the odds ratio of unfavorable outcomes is two times more after ESE but not ES.

**How does this paper help me reach a conclusion about how to treat the patient in my vignette?** This answer is not altogether straightforward.

While methodologically strong, the authors represented ES as a categorical variable (present or absent) and defined ESE as single continuous ES lasting 30 minutes or repeated ES occupying 30 minutes out of a 60-minute epoch on CEEG. However, the new ACNS guideline defines ESE as ES occupying 20% of an hour or  $\geq 10$  minutes of continuous ES in a 60 minute epoch.<sup>9</sup> For now, we do not know the incidence of conversion of ES to ESE and therefore the number of ES per hour that should trigger escalation of treatment to avoid ESE remains a clinical decision. Additionally, treatment of impending ESE is not uniform across all centers.

At the authors' hospital, treating physicians used ASM once ES/ESE was identified on CEEG and yet outcomes in these treated ESE patients were unfavorable. Therefore, should one conclude that presence of ESE itself predicts unfavorable outcomes and hence aggressive treatment of ESE should be tempered? Alternatively, should one conclude that treating every single ES is not warranted because it does not affect outcome or mortality? Are there other biomarkers that we should target?

The takeaway message for my patient is that while I monitor the seizure frequency from one hour to the next, it may not be critical to hit every seizure hard. Clearly, more prospective studies that categorize ES exposure uniformly and have evidence-based management strategies will allow for uniform short- and long-term outcome assessments.

By Charuta Joshi

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