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Development and validation of a seizure prediction model in critically ill children

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ABSTRACT

Purpose: Electrographic seizures are common in encephalopathic critically ill children, but identification requires continuous EEG monitoring (CEEG). Development of a seizure prediction model would enable more efficient use of limited CEEG resources. We aimed to develop and validate a seizure prediction model for use among encephalopathic critically ill children.
Method: We developed a seizure prediction model using a retrospectively acquired multi-center database of children with acute encephalopathy without an epilepsy diagnosis, who underwent clinically indicated CEEG. We performed model validation using a separate prospectively acquired single center database. Predictor variables were chosen to be readily available to clinicians prior to the onset of CEEG and included: age, etiology category, clinical seizures prior to CEEG, initial EEG background category, and inter-ictal discharge category.
Results: The model has fair to good discrimination ability and overall performance. At the optimal cut-off point in the validation dataset, the model has a sensitivity of 59% and a specificity of 81%. Varied cut-off points could be chosen to optimize sensitivity or specificity depending on available CEEG resources.

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Conclusion: Despite inherent variability between centers, a model developed using multi-center CEEG data and few readily available variables could guide the use of limited CEEG resources when applied at a single center. Depending on CEEG resources, centers could choose lower cut-off points to maximize identification of all patients with seizures (but with more patients monitored) or higher cut-off points to reduce resource utilization by reducing monitoring of lower risk patients (but with failure to identify some patients with seizures).

1. Introduction

Electrographic seizures (ES) are reported in 10–50% of children with acute encephalopathy who undergo continuous EEG monitoring (CEEG),[1–19] and there is increasing evidence that high ES burdens are associated with worse outcomes, even in models that adjust for acute encephalopathy etiology and severity.[10,13,17,20,21] Most ES in critically ill children have no clinical correlate so CEEG is required for identification,[3,6,8–10,12–15,18,19] leading to recent increases in CEEG use within pediatric intensive care units (PICUs).[22] CEEG is resource intense, and seemingly small changes in CEEG utilization may have substantial impacts on equipment and personnel needs.[23] Seizure prediction models could allow CEEG to be targeted to children at highest risk for experiencing ES within the resource limitations of an individual medical center.

Several studies have described clinical and EEG risk factors for ES. However, these data are limited in several ways. First, the data are obtained from patients who have undergone CEEG at single or few institutions,[3,7–9,11,12,14,17,18] so the risk factors identified may not be useful if implemented at a different institution with different patient characteristics or CEEG practice. Although multi-center consortia are starting to study ES epidemiology,[13,24,25] multi-center data variability might preclude meaningful application at individual centers. Second, prior studies have not combined the identified risk factors to create clinically useful ES prediction models accounting for multiple risk factors. Currently, a clinician may consider multiple known seizure risk factors (such as younger age, prior convulsive seizures, and inter-ictal epileptiform discharges) when making a clinical judgment regarding the need for CEEG, but there are no data available to help determine the accuracy of this combinatorial approach.

We aimed to determine whether an ES prediction model developed from retrospective multi-center data could be used to predict ES occurrence when applied to data obtained from a single center.

2. Methods

2.1. Datasets

The model was created and validated using separate datasets of children in PICUs who underwent clinically indicated CEEG. The overall study was approved by The Children's Hospital of Philadelphia institutional review board, and submission of data was approved by the institutional review boards at each site.

The model creation dataset was derived from a multi-center study in which 11 sites each collected data by retrospective chart review on 50 consecutive critically ill children to yield 550 subjects.[13,24,25] The 11 sites were large academic medical centers with available pediatric neurology consultation and CEEG. Subjects had undergone clinically indicated CEEG as dictated by practice patterns at each institution and not any study protocol or national guideline. Thus, these subjects were heterogeneous in terms of etiology, degree of encephalopathy, and other clinical characteristics. For the current study, we excluded 214 subjects with pre-existing epilepsy-related diagnoses leading to PICU admission, leading to a cohort of 336 subjects. Patients with epilepsy were excluded for several reasons. Prior classification proposals have differentiated between non-convulsive status epilepticus (NCSE) as occurring in the context of acute brain injury (termed "comatose NCSE") and occurring in the context of more benign epilepsy conditions (termed "NCSE proper") since the relative impact of seizures to overall prognosis differs.[26] Our aim was to address the use of CEEG when screening for electrographic seizures in patients with acute encephalopathy in whom seizure identification and management might serve as a neuroprotective strategy. Second and more practically, institutional practice, bed availability, and admission time of day likely impact decisions regarding whether patients with epilepsy in need of CEEG are admitted to the epilepsy monitoring unit or PICU. Data were obtained by chart review from the reports created by trained encephalographers on-service when the CEEG was obtained and the tracings were not re-interpreted for this study.

The model validation dataset was derived from a prospective single center dataset from The Children's Hospital of Philadelphia and included 222 subjects who underwent CEEG while in the PICU without an epilepsy-related diagnosis prior to admission. As described above, patients with epilepsy were excluded. Institutional practice at The Children's Hospital of Philadelphia is to obtain at least one day of CEEG in any patient admitted to the PICU with encephalopathy of any degree and any acute neurologic condition (i.e. traumatic brain injury, stroke, hypoxic ischemic encephalopathy, encephalitis). These were different subjects than those contributed by The Children's Hospital of Philadelphia to the multi-center model creation dataset. Epidemiologic data from a portion of this dataset have been published previously.[18] The single center validation data were obtained prospectively by one investigator (N.S.A.) who re-scored the CEEG after clinical interpretation for seizure category and background category while blind to clinical data other than age.

We categorized subjects by ES category (none, electrographic seizures, electrographic status epilepticus). Electrographic status epilepticus was defined as a single or recurrent electrographic seizure(s) lasting 30 min or more within a 1 hour epoch. We collected data regarding clinical variables previously identified as predicting an increased risk of experiencing ES. Age was classified as $>$24 months or $\leq$24 months. Clinically evident seizures prior to CEEG were classified as present or absent. Etiology category was classified as structural (i.e. traumatic brain injury, stroke (ischemic or hemorrhagic), hypoxic-ischemic encephalopathy, encephalitis, posterior reversible leukoencephalopathy) or non-structural (hepatic encephalopathy, sepsis, metabolic disorders). The initial 1 h EEG background categorization (normal/sleep, slow-disorganized, discontinuous, burst-suppression, or attenuated/featureless), and initial one hour EEG inter-ictal epileptiform discharge (IED) categorization (present or absent). This background categorization scheme has been used in prior studies related to EEG in critically ill children.[13,20,21] When EEGs from critically ill children are reviewed by pediatric encephalographers, inter-rater agreement for background features continuity (continuous, discontinuous, flat) and