Frequency and Predictors of Nonconvulsive Seizures During Continuous Electroencephalographic Monitoring in Critically Ill Children

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Objective: To determine the incidence, predictors, and timing of nonconvulsive seizures (NCSz) during continuous electroencephalographic monitoring (cEEG) in critically ill children.

Methods: We identified critically ill children who underwent cEEG during a 4-year period. Multivariate logistic regression analysis was performed to determine variables associated with NCSz.

Results: Among 117 monitored children, 44% had seizures on cEEG and 39% had NCSz. The majority of patients with seizures (75%) had purely NCSz, and 23% of patients had status epilepticus, which was purely nonconvulsive in 89% of cases. Seizures occurred immediately on cEEG initiation in 15%, within 1 hour in 50%, and within 24 hours in 80%. Those with clinical seizures prior to cEEG were more likely to have NCSz on cEEG (83%) than those without prior seizures (17%). On multivariate analysis, NCSz were associated with periodic lateralized epileptiform discharges and absence of background reactivity.

Conclusions: Seizures, the majority being NCSz, are common during cEEG in critically ill children (seen in 44% of patients). Half are detected in the first hour of recording, whereas 20% are not detected until after more than 24 hours of recording. Nonconvulsive seizures are associated with periodic lateralized epileptiform discharges and absence of reactivity on cEEG. This study confirms the importance of prolonged cEEG for critically ill children as a means to detect NCSz.

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METHODS

STUDY POPULATION

We identified all patients younger than 18 years in an ICU who underwent cEEG at Columbia University Medical Center, New York–Presbyterian Hospital, between June 1, 2000, and April 30, 2004. We defined any patients admitted into an ICU as critically ill, regardless of etiology. Patients were identified using (1) the Department of Neurology cEEG log; (2) the Epilepsy Division log containing all cEEG reports for that period; and (3) a computerized search of the hospital clinical information system for patients who underwent cEEG. A complete list of all patients undergoing cEEG was compiled by cross-referencing the 3 sources. We excluded patients for whom the primary indication of cEEG was therapeutic; that is, for titration of intravenous medication to treat refractory SE or elevated intracranial pressure. Accordingly, only patients for whom the primary indication for cEEG was diagnostic (ie, for detection of possible subclinical seizures or for the evaluation of unexplained diminished consciousness) were included. There is some overlap between patients in this study and those in our prior study.1 However, fewer than half of the children in this study (53 [45%] of 117) were included in the prior analysis of 571 patients of all ages, and more than 90% (517/570) of patients in the prior study were not included in this study.

DATA COLLECTION

All clinical data were gathered from medical record review, cEEG reports, discharge summaries, and computerized daily physician notes. Baseline demographic data (age and sex), medical history (including but not limited to epilepsy, stroke, brain tumor, and neurosurgical procedures), and the location of the patient at the time of cEEG (non-ICU hospital ward, neurosciences ICU, pediatric or neonatal ICU, or medical, cardiothoracic, or surgical ICU) were recorded. On the basis of medical record information, one of the study neurologists (N.J.) retrospectively determined the neurologic status of patients at the time monitoring was initiated (awake, lethargic or stuporous, or comatose) and the presence or absence of any convulsive seizures (CSz) during the current illness prior to cEEG. Primary admission diagnoses included epilepsy-related seizures, ischemic stroke, subarachnoid hemorrhage, nontraumatic parenchymal intracerebral hemorrhage, traumatic brain injury, brain tumor, toxic-metabolic encephalopathy, central nervous system infection, hypoxic-ischemic encephalopathy, status postneurosurgery, and unexplained decrease in level of consciousness.

Continuous electroencephalographic monitoring was performed digitally using 21 electrodes placed according to the International 10-20 System12 (except in some postneurosurgical cases in which a limited montage had to be used owing to hardware placement and surgical wounds). Most ICU patients at Columbia University Medical Center are ready to undergo cEEG within about 2 hours (approximate range, 1-12 hours). Recordings were not viewed continuously but were reviewed at least twice daily, and additionally as needed or if requested by physicians. To determine clinical correlates for episodes of electrographic seizures, contemporaneous video recordings were used. The presence of CSz and NCSz as documented by the cEEG report was recorded, and medical record review, discharge summaries, and physician notes provided additional information. Electrographic seizures were defined as rhythmic discharges or a spike-and-wave pattern with definite evolution in frequency, location, or morphologic features lasting at least 10 seconds; evolution in amplitude alone did not qualify.16 Seizures were considered convulsive if any of the following was described: "generalized tonic-clonic seizures," "grand mal seizures," "convulsions," "rhythmic jerking," "rhythmic twitching," or similar descriptions. If none of these were present and cEEG confirmed seizures, the seizures were considered nonconvulsive. We recorded the number of continuous hours of cEEG and categorized the time of cEEG until the first seizure as follows: present at the start of cEEG; within 1 hour; between hours 1 and 6, 6 and 12, or 12 and 24; during day 2; between days 2 and 7; and after 7 days of monitoring. We recorded the presence of any periodic epileptiform discharges (PEDs) including periodic lateralized epileptiform discharges (PLEDs), generalized PEDs, and bilateral independent PLEDs. The presence of triphasic waves, frontal intermittent rhythmic delta activity (FIRDA), or suppression-burst activity was also documented.

STATISTICAL ANALYSIS

Data were analyzed using commercially available statistical software (SPPS version 12.0, SPPS Inc, Chicago, Ill). A univariate analysis was conducted to identify significant associations between a variety of variables and the presence of NCSz using x2 analysis and the Fisher exact test if appropriate. Associated variables were then identified using forward stepwise logistic regression analysis. Significance was judged at the P=.01 level owing to multiple comparisons. Trend was defined as P=.01 to .10.

RESULTS

STUDY COHORT

We monitored 117 patients in the pediatric or neonatal ICU between June 1, 2000, and April 30, 2004. Mean age was 4.8±0.5 years, with a range of 1 day to 18 years, and 53% (n=62) were male. Mean length of ICU stay was 24.0±2.7 days. The most common admission diagnoses for patients undergoing cEEG were epilepsy-related seizures and unexplained decreased mental status (Table 1). The 2 main indications for cEEG were unexplained coma (n=100; 86%) and epilepsy evaluation (n=10; 9%).

SEIZURES PRIOR TO AND DURING cEEG

Seizures were recorded during cEEG in 51 (44%) of 117 patients. Most patients, 75% (38/51), had NCSz only, whereas 16% (8/51) had both NCSz and CSz, and 5 (10%) of 51 patients had CSz only. Status epilepticus was recorded in 27 (23%) of 117 patients. Of these 27 patients, 89% (n=24) had NCSE only, and 11% (n=3) had both NCSE and GCSE. Eighty-two (70%) of 117 patients had in-hospital seizures prior to cEEG initiation. Of those who had clinical seizures in the hospital prior to cEEG, 91% (75/82) had CSz and 22% (18/82) had GCSE prior to being prepared for cEEG. Figure 1 shows the frequency of seizures by age group, before or during cEEG.

CLINICAL FACTORS ASSOCIATED WITH NCSz

None of the clinical variables were significantly associated with NCSz on cEEG (Table 2). However, a history of epilepsy, in-hospital seizures prior to cEEG, or stupor or coma at the time of cEEG initiation showed...
trends toward significance in the univariate analysis (.01 < P < .10). Recent hypoxic injury showed a trend toward a lower incidence of NCSz.

**TIME TO RECORD SEIZURES ON cEEG**

Seizures were detected in the first hour of recording in 50% of the 51 patients who eventually had seizures recorded by cEEG (Figure 2). Of these patients, 80% had a seizure detected within 24 hours of recording and 87% within 48 hours; 15% had a seizure immediately on cEEG initiation (eg, first seizure started before cEEG began and was ongoing).

### ELECTROGRAPHIC PATTERNS ASSOCIATED WITH NCSz ACTIVITY ON cEEG

We evaluated 11 electrographic patterns, including seizures, periodic discharges, and background patterns such as reactivity, for their association with NCSz. In all patients, reactivity of the EEG background indicated reactivity to auditory, noxious, or other types of external stimuli. In the multivariate analysis, the presence of PLEDs (P = .008; odds ratio [OR] = 7.0; 95% confidence interval [CI], 1.7-29.5) and lack of background reactivity (P < .001; OR = 12.2; 95% CI, 4.0-37.0) were the only electrographic features independently associated with the presence of NCSz on cEEG. Eleven (73%) of 15 patients with PLEDs detected by cEEG had NCSz compared with 35 (34%) of 102 patients without PLEDs. Twenty-eight (65%) of 43 patients without background reactivity on cEEG had NCSz compared with 17 (24%) of 70 patients with background reactivity. Four (80%) of 5 patients who had PLEDs and absence of reactivity had NCSz on cEEG, whereas only 10 (17%) of 60 patients who had neither of these 2 predictive factors had NCSz on cEEG. The chance of having an NCSz if PLEDs alone were present (but with reactivity) was 70%, whereas it was 63% if absence of reactivity alone (without PLEDs) was present. The presence of CSz or GCSE while the patient was undergoing cEEG, the presence of any PEDs or FIRDA, absence of state changes, and absence of sleep architecture all showed a trend (.01 < P < .10) toward significance but were not independently associated with the presence of NCSz on cEEG in the multivariate analysis.
Variables associated with NCSz in patients younger than 2 years (n = 53) included in-hospital seizures (OR = 14.8; 95% CI, 2.3-95.9; NCSz seen in 54% of patients with in-hospital seizures vs 17% without) and absence of sleep architecture (OR = 19.9; 95% CI, 3.6-111.0; 74% vs 18%). For patients 2 years or older (n = 64), variables associated with NCSz included in-hospital seizures (OR = 8.9; 95% CI, 2.1-37.2; 53% vs 20%) and absence of reactivity (OR = 6.7; 95% CI, 1.7-27.5; 57% vs 27%).

**OUTCOME**

Fourteen percent (16/116; variable missing in 1 child) of children in this study died. Mortality was not associated with seizures during cEEG. Nine (18%) of 50 children with electrographic seizures died compared with 7 (11%) of 65 children without electrographic seizures.

The entire statistical analysis was reanalyzed excluding children included in the prior study of all age groups from our center. After excluding the earlier patients, PLEDs were no longer a predictor of seizures on cEEG. In this retrospective study of 117 critically ill children who underwent cEEG, seizures were recorded in 51 (44%) of 117 subjects. The vast majority of these patients (75%) had purely NCSz, which would not have been diagnosed without cEEG. An additional 8 patients (16%) had both CSz and NCSz. Overall, 50% of patients had their first seizure detected within 1 hour of recording, but 20% of seizures were not detected until after more than 24 hours of recording. Nonconvulsive seizures were most common in those with PLEDs (73%; P = .008), absence of reactivity on EEG (65%; P < .001), any periodic discharges (65%; P = .03), absence of sleep architecture (50%; P = .04), and clinical seizures prior to cEEG (46%; P = .02).

**COMMENT**

The main objective of the prior study was to examine not the...
pediatric experience but the overall experience in all age groups. Children represented only 13% of that sample. We felt that it was important to analyze children separately and report our overall pediatric experience, including all monitored children, in part because seizure etiologies and EEG patterns may vary significantly between children and adults and may thus yield different predictors of seizures on cEEG. The predictors of NCSz did not change significantly when the earlier children were excluded except that PLEDs were no longer significantly associated with NCSz on cEEG owing to the smaller number of cases.

The frequency of electrographic seizures in this study of critically ill children undergoing cEEG is within the estimated range of 20% to 50% from other studies, which primarily included adults. The seizure detection rate is obviously highly dependent on the selection of patients undergoing cEEG. Nonetheless, the strikingly high incidence of clinically inapparent seizures detected in critically ill children undergoing cEEG suggests that similar seizures have likely gone undetected and untreated in other critically ill children. We strongly suspect that although cEEG is readily available at our center, this technology is not yet uniformly utilized.

Most patients in whom seizures were detected by cEEG (75%) had purely NCSz, emphasizing the importance of cEEG in critically ill children with an acute neurologic insult or another medical illness and concurrent mental status change. In our study, NCSz were defined as seizures that would otherwise go unnoticed without cEEG. Another study found that 27% of patients (all age groups) presenting to an emergency department with an altered level of consciousness were found to be in NCSE when undergoing emergency EEG. There were no overt clinical signs, and the presentation was not predictive of NCSE in most of these patients. The diagnosis of NCSE would have been delayed or missed had EEG not been performed. One group looked at seizures in infants who had undergone routine EEG and found that only 21% of seizures were associated with clinical manifestations. Another study reported that 70% of adult comatose patients with NCSz had only subtle motor movements, and 10% had no clinical signs. The clinical utility and prognostic importance of cEEG with video in neurologic and neurosurgical ICUs has also been studied in patients aged 16 years and older. In that study, 18% of patients had NCSE. Another group recruited 275 full-term and preterm infants into a prospective 4-channel EEG monitoring study. They found electrographic seizures in 55 infants. Clinical signs were simultaneous in 12, limited in 20, and absent in the remaining 23. Interestingly, outcome was not affected by the presence of clinical signs at the time of the seizures. It is clear that most seizures in critically ill patients are NCSz and can be diagnosed only with EEG.

All critically ill children who underwent cEEG during a 4-year period were included in this study, regardless of admission diagnosis or whether or not they had had a clinical seizure. It is therefore plausible that certain etiologies may predispose to seizures but that the number of patients in each category was too small to reach significance in the logistic regression analysis in predicting NCSz. A prior larger study including all ages at our center found that a history of epilepsy was a predictor of electrographic seizures. This effect was not reproduced in this study in the multivariate analysis. Furthermore, it is well known that NCSE can follow GCSE. Three of 18 children presenting with refractory SE in our study went on to have NCSE on cEEG. One hundred sixty-four patients admitted with CSE were prospectively followed up in another study and underwent cEEG for a minimum of 24 hours after the clinical onset of their seizures; 48% of them had electrographic seizures on cEEG, and 14% had NCSE. All of the patients with NCSE were comatose and did not show any clinical signs of seizures. In the Veterans Affairs Status Epilepticus Cooperative Study, 20% of patients with overt GCSE who were believed to have received adequate treatment continued to have NCSz or NCSE on EEG. Finally, the retrospective nature of our study makes it impossible to accurately predict the risk of electrographic seizures in various disorders, since all patients with a particular diagnosis admitted to an ICU would have to undergo cEEG, whether or not they were suspected of having seizures, to determine the incidence by etiology. This study was primarily designed to look at the overall comprehensive experience at our center with this diagnostic tool in critically ill children to guide us in the clinical use of cEEG in this population.

In our study, 80% of seizures were detected within the first 24 hours. This finding is consistent with a previous study at our center in patients of all ages, in which seizures were detected within the first 24 hours of cEEG in 88% of all patients who eventually went on to have seizures detected by cEEG. It is unlikely that a seizure detected beyond 24 hours of cEEG is the primary cause of a patient’s altered mental status. In that case, it is more likely that another underlying condition is contributing to the patient’s poor cognitive state, although it may still be important to know whether the patient is continuing to have intermittent seizures.

Variables found to be associated with NCSz in our study included the presence of PLEDs and absence of background reactivity on cEEG. A prior study at our center in patients of all ages found that Csz prior to cEEG commencement were predictive of electrographic seizures on cEEG; 21% of patients with PLEDs had their first seizure after the first 24 hours of cEEG compared with 8% of those without PLEDs. This analysis could not be done in this study because of the small number of patients who had seizures detected after 24 hours. However, it may be warranted to continue cEEG beyond 24 hours in those without electrographic seizures but with PLEDs, knowing that they seem to be associated with seizures. Finally, it is not surprising that absence of reactivity may be associated with NCSz, since patients without background reactivity on cEEG may have more cerebral dysfunction overall, predisposing them to both NCSz and poor reactivity. Similar results were obtained in adults. Although no prospective studies have examined the long-term effects of NCSz or NCSE in critically ill children, one study in adults with intracerebral hemorrhage found an association between NCSz and increased edema and midline shift, with a trend toward worse outcome.
Nonconvulsive seizures are very common during cEEG in the pediatric population, with 44% of children having seizures detected on cEEG, of whom 38 (75%) had NCSz only. Only half are detected in the first hour of recording, and one fifth of seizures are not recorded until after more than 24 hours of monitoring. This study demonstrates the importance of prolonged EEG for critically ill children at risk for seizures as a means to detect NCSz and strongly suggests that many patients with NCSz and NCSE are being missed, even at our tertiary center with a large cEEG program. Nonconvulsive seizures in children are associated with PLEDs, absence of EEG reactivity, and possibly seizures prior to cEEG initiation, any periodic discharges, and absence of sleep architecture. Children with PLEDs or absence of reactivity on cEEG should be monitored for at least 24 hours and maybe longer to ensure that they are not having NCSz. Future prospective studies are needed to confirm these findings as well as to determine the prognostic and treatment implications of NCSz in children.

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