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Prevalence of nonconvulsive status epilepticus in comatose patients

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Article abstract—Background: Nonconvulsive status epilepticus (NCSE) is a form of status epilepticus (SE) that is an often unrecognized cause of coma. Objective: To evaluate the presence of NCSE in comatose patients with no clinical signs of seizure activity. Methods: A total of 236 patients with coma and no overt clinical seizure activity were monitored with EEG as part of their coma evaluation. This study was conducted during our prospective evaluation of SE, where it has been validated that we identify over 95% of all SE cases at the Medical College of Virginia Hospitals. Only cases that were found to have no clinical signs of SE were included in this study. Results: EEG demonstrated that 8% of these patients met the criteria for the diagnosis of NCSE. The study included an age range from 1 month to 87 years. Conclusions: This large-scale EEG evaluation of comatose patients without clinical signs of seizure activity found that NCSE is an under-recognized cause of coma, occurring in 8% of all comatose patients without signs of seizure activity. EEG should be included in the routine evaluation of comatose patients even if clinical seizure activity is not apparent. Key words: Nonconvulsive status epilepticus—Coma—EEG.

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EEG monitoring for seizure activity is only performed in most medical centers in the evaluation of coma when overt seizures are observed in comatose patients. Nonconvulsive status epilepticus (NCSE) can present in comatose patients with no overt signs of seizure activity and may represent an under-recognized form of coma. A major concern is that unless EEGs are routinely performed to evaluate the possibility of NCSE in comatose patients, the diagnosis of NCSE will be missed. No large-scale studies of EEG evaluation in comatose patients without clinical signs of seizure activity have been published.

We evaluated the frequency of NCSE in patients who were admitted to intensive care units (ICU) for coma with unresponsiveness, but without overt seizure activity. In addition, this study was initiated to establish clinical guidelines and the utility of routine EEGs in the evaluation of comatose patients who exhibit no clinical signs of seizure activity.

Methods. We reviewed the Medical College of Virginia EEG database. Using our computerized text database, patients with coma were identified and a retrospective review of their EEGs was performed. All patients met the following criteria: 1) admission or transfer to an ICU, 2) altered mental status meeting the definition of coma, 3) no overt seizure activity, and 4) at least 30 minutes of recorded continuous EEG. A subset of these patients was classified as having NCSE. Patients were categorized as having NCSE only if 1) they fulfilled the criteria for SE, defined as continuous or nearly continuous electrographic seizure activity lasting at least 30 minutes without clinical seizure activity; and 2) at least two EEG interpreters independently agreed that the pattern represented seizure activity. Therefore, we had one group of cases of coma without SE, and one group with NCSE.

This study was conducted on Medical College of Virginia Hospitals (MCVH) patients during the simultaneous prospective analysis of SE at MCVH. The MCVH SE studies1–4 were validated for ascertainment of SE. In these studies, SE was identified in over 95% of the cases within the hospital. This high identification rate was made possible by the extensive in-house education program for seizure recognition. This included ER staff, ICU personnel, house staff, physicians, nurses, and emergency medical technicians. Thus, in this database, both overt and subtle clinical seizure activity was identified with a high level of accuracy. Although it is impossible to be completely certain that each comatose case with NCSE had no clinical seizure activity, this database represents one of the most accurate evaluations of SE and seizure activity in comatose patients based on demonstrated validation studies.1–4

EEGs were obtained in all of these patients within the first 3 days of making the diagnosis of coma and
were obtained to evaluate the level of brain function rather than to evaluate overt seizure activity. The EEG criteria for NCSE consisted of discrete electrographic seizures, continuous spike and wave activity, or rhythmic recurrent epileptiform activity. These demonstrated marked improvement with the injection of an IV benzodiazepine. All recordings were performed on an 18 to 22 channel EEG instrument using the International 10-20 system of electrode placement. All patients who presented with generalized tonic-clonic SE or overt seizure activity were excluded. Clinical manifestations were evaluated by reviewing the patients’ records.

We evaluated outcome in terms of mortality for the hospitalization during which the EEG was performed. Outcome data were obtained directly from the hospital computer database and by checking names and social security numbers in the Health Department’s vital statistics database.

Results. A total of 236 cases were identified that fulfilled the inclusion criteria for this study. These patients all met

Figure 1. Age distribution. SE = status epilepticus.

Figure 2. Race and gender distribution. SE = status epilepticus.

Figure 3. Generalized nonconvulsive status epilepticus. Bifrontally predominant 1-Hz rhythmic sharp and slow wave complexes.
the criteria for diagnosis of coma without overt seizure activity or clinical signs of seizures. A total of 217 cases had coma without SE; 19 cases (8%) had coma and NCSE.

The age distribution for coma patients with and without SE is shown in figure 1. Children (1 month through 15 years of age) comprised 11% of the patients and the remaining 89% of the patients were 16 years of age or older. The adult population was divided into young adult (51%) and elderly (38%), defined as age 60 or older. Nineteen cases or 8% of the total comatose population fulfilled the criteria for electrographic SE. There was no significant age distribution difference between the two populations. In the patients with NCSE, age ranged from 5 weeks to 79 years. In coma patients without SE, age ranged from 8 months to 87 years.

The distribution of gender and race of the two populations is presented in figure 2. The results demonstrate that there were more women than men in the SE versus the non-SE coma group, and no statistically significant difference in race distribution between the SE and non-SE coma groups.

Representative EEGs are demonstrated in figures 3 and 4. The EEG characteristics of the 19 coma cases with SE are presented in the table. By definition, epileptiform discharges were present in 100% of the EEGs of patients with SE. In addition to electrographic seizure activity, EEG findings included a mixture of delta activity and burst suppression. Epileptiform discharges occurred in 5% of the EEGs of comatose patients who were not in SE. Most of the EEGs of patients in coma without SE demonstrated a mixture of delta and theta activities consistent with an electrographic diagnosis of encephalopathy. In many cases the burst suppression was secondary to the administration of antiepileptic drugs (AEDs). Theta and alpha coma accounted for approximately 8% of the patients not in SE and 0% of the patients with SE. Periodic lateralizing epileptiform discharges (PLEDs) were present in both groups, and by themselves were not considered to be SE for the purpose of this analysis. The EEG was useful in both groups, in diagnosing either bilateral cortical dysfunction or subclinical seizure activity.

Etiology of SE was defined as the immediate precipitating cause of the patient's condition. Figure 5 demonstrates the etiologies of coma with SE and without SE. Hypoxia/anoxia was the most common etiology, occurring in 42% of the patients with SE. The second most common etiology was cerebrovascular accident (CVA) (22%), followed by infection (5%), head trauma (5%), metabolic disorders (5%), withdrawal from alcohol or AED (5%), and tumor (5%). The etiology was unknown in 11% of the NCSE group. The distribution of etiologies for coma patients not in SE was similar to the distribution of etiologies of patients in NCSE. Hypoxia/anoxia was the most common etiology (27%), followed by unknown (17%), head trauma (17%), CVA (13%), metabolic disorders (15%), infection (5%), withdrawal from alcohol or AED (4%), and tumor (1%).

Of the coma patients with SE, 53% survived and 47% died during the hospitalization. Of the coma patients with-
Discussion. Generalized convulsive SE is the most common form of SE. However, any seizure type may present as SE. NCSE is an important SE type that may present as absence, complex partial, or electrographic SE. In a prospective, population-based study of SE, NCSE represented approximately 5% of SE cases presenting in Richmond, Virginia. NCSE also appears in a relatively high percentage of comatose patients without any obvious signs of seizure activity. In the current study, 236 EEGs were performed in ICUs to evaluate comatose patients with no clinically overt seizure activity. Nineteen patients (8%) were found to be in NCSE. SE may be underdiagnosed in comatose patients, resulting in suboptimal management and outcome. This study demonstrates that bedside EEGs are effective in the evaluation of the clinically ambiguous comatose ICU patient, and essential for accurate diagnosis of NCSE.

Other investigators have studied non–tonic-clonic SE in patients with altered consciousness. Privitera et al. prospectively studied hospitalized patients with altered consciousness who had EEG to evaluate possible non–tonic-clonic SE. Of 198 cases with altered consciousness but no clinical convulsions, 37% showed EEG and clinical evidence of definite or probable NCSE. In 23 SE cases, altered consciousness was the only clinical sign at the time of diagnosis, with subtle motor activity present in 36 others. Neither clinical signs nor prior history predicted which patients demonstrated SE on EEG. Lowenstein and Aminoff reported 38 patients in non–tonic-clonic SE and concluded that the majority of patients with subtle motor activity and depressed consciousness had EEG findings of SE, and that EEG was necessary to diagnose this condition. A prospective study performed by Altafullah et al. revealed 19 subtle generalized SE cases in a 24-month time period. In each of these studies, subjects were selected after NCSE had been diagnosed on EEG, or were selected for EEG owing to high clinical suspicion of NCSE, based on altered consciousness, prolonged alteration of consciousness following a generalized tonic-clonic seizure, or subtle motor activity. The current study is the first to assess the prevalence of NCSE in a broad

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Frequency (Hz)</th>
<th>Persistence</th>
<th>Distribution</th>
<th>Morphology</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 wk/M</td>
<td>2</td>
<td>Brief breaks</td>
<td>Bilateral independent</td>
<td>Periodic discharges then polyspike and wave</td>
<td>Head trauma</td>
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<tr>
<td>12 y/F</td>
<td>1–2</td>
<td>Brief breaks</td>
<td>Generalized</td>
<td>Sharp and rhythmic slow waves</td>
<td>Unknown</td>
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<tr>
<td>18 y/M</td>
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<td>Continuous</td>
<td>Generalized</td>
<td>Spikes and sharp waves</td>
<td>Tumor</td>
</tr>
<tr>
<td>21 y/M</td>
<td>4.5 then 2</td>
<td>Brief breaks</td>
<td>Right frontal</td>
<td>Monomorphic rhythmic theta activity</td>
<td>Anoxia</td>
</tr>
<tr>
<td>31 y/F</td>
<td>3–6</td>
<td>Continuous</td>
<td>Right central parietal</td>
<td>Spikes and slow waves</td>
<td>Drugs</td>
</tr>
<tr>
<td>34 y/M</td>
<td>1–2</td>
<td>Intermittent</td>
<td>Bifrontal</td>
<td>Spikes and sharp waves</td>
<td>Anoxia</td>
</tr>
<tr>
<td>41 y/M</td>
<td>3–4 then 1.5–2</td>
<td>Intermittent</td>
<td>Generalized</td>
<td>Rhythmic slow waves then polyspike and wave</td>
<td>Infection</td>
</tr>
<tr>
<td>43 y/M</td>
<td>3–4</td>
<td>Brief breaks</td>
<td>Generalized</td>
<td>Spike and wave</td>
<td>Anoxia</td>
</tr>
<tr>
<td>52 y/F</td>
<td>1–2</td>
<td>Intermittent</td>
<td>Generalized</td>
<td>Rhythmic sharp discharges</td>
<td>Anoxia</td>
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<tr>
<td>57 y/M</td>
<td>1–2</td>
<td>Continuous</td>
<td>Bifrontal, maximal left</td>
<td>Spikes and rhythmic sharp waves</td>
<td>CVA</td>
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<tr>
<td>58 y/M</td>
<td>3–4</td>
<td>Brief breaks</td>
<td>Generalized</td>
<td>Spike and wave</td>
<td>Anoxia</td>
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<tr>
<td>60 y/F</td>
<td>5–7</td>
<td>Continuous</td>
<td>Left hemisphere, maximal parietal occipital</td>
<td>Spikes and sharp waves</td>
<td>CVA</td>
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<tr>
<td>62 y/F</td>
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<td>Continuous</td>
<td>Generalized</td>
<td>Spikes and sharp waves</td>
<td>Unknown</td>
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<td>66 y/F</td>
<td>11–14 then 2–4</td>
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<td>Left hemisphere w/secondary generalization</td>
<td>Rhythmic fast then slow waves</td>
<td>Anoxia</td>
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<td>70 y/F</td>
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<td>Anoxia</td>
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<tr>
<td>70 y/F</td>
<td>5–1</td>
<td>Brief breaks</td>
<td>Generalized</td>
<td>Sharp and slow waves</td>
<td>Metabolic</td>
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<tr>
<td>70 y/F</td>
<td>3–4</td>
<td>Intermittent</td>
<td>Left hemisphere</td>
<td>Spikes and sharp waves</td>
<td>CVA</td>
</tr>
<tr>
<td>78 y/F</td>
<td>4–5</td>
<td>Brief breaks</td>
<td>Bilateral independent</td>
<td>Spike and polyspike and wave discharges</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>79 y/F</td>
<td>2</td>
<td>Brief breaks</td>
<td>Left hemisphere w/secondary generalization</td>
<td>Spike and wave</td>
<td>CVA</td>
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CVA = cerebrovascular accident.
The implications of the term NCSE are controversial. Gastaut, Treiman, Krumholz, and others have used the term to refer only to absence or complex partial SE.12,13,28 Gastaut suggested that the term absence SE be applied to all cases of generalized NCSE that lack focal electromyographic findings. This definition led to the initial belief that absence SE comprised the majority of NCSE, whereas complex partial SE was relatively rare. However, Tomson et al.29 have shown that complex partial SE may rapidly generalize, making later-stage complex partial SE electromyographically indistinguishable from absence SE. With prolonged EEG monitoring, examples of generalized electrographic SE have demonstrated initial focal onset or waxing and waning focal features. These cases, which might previously have been considered absence SE, have been appropriately recognized as complex partial SE with secondary generalization.

As more clinical and electrographic cases of NCSE have been described in the literature, the need for a widely accepted and unambiguous NCSE definition and classification scheme has become increasingly clear. Brodtkorb et al.30 have proposed the following classification of NCSE: 1) NCSE in generalized epilepsy syndromes; 2) NCSE in localization-related epilepsy with localized EEG features, generalized EEG features, or transitional EEG features; and 3) undetermined form of NCSE. Most recently, Kaplan31 has stratified NCSE into 1) localization-related NCSE, 2) generalized NCSE, and 3) indeterminate or intermediate NCSE. Under each of these headings, determined by EEG or clinical criteria, there are three subcategories that describe the clinical state: mild—patient conversant and interactive, but confused; moderate—patient lethargic, follows at least one-step commands; and coma—no meaningful verbal or motor interaction, limbs withdraw or posture to pain. This stratification system is broad enough to include SE of focal onset, primary and secondarily generalized SE, and those forms of electrographic SE that are not easily categorized. They are specific enough to form a common frame of reference among clinicians and electroencephalographers when SE is assessed. NCSE in coma, which includes a heterogeneous group of EEG patterns, fits into categories 1, 2, and 3 in this classification system, with subcategory “coma” denoting the comatose clinical state.

This study demonstrates that as many as 8% of comatose patients without clinical seizure activity had NCSE that would not have been detected without EEG analysis. This percentage is lower than the previous studies of NCSE in coma have suggested.25-27 In this study, the EEGs were selected not because the patients were suspected to be in NCSE, but because they were comatose. It is also possible that some of our patients may have been in NCSE that stopped before the EEG and manifested only a non-ictal pattern such as PLEDs or bi-PLEDs during the EEG. In addition, our findings may not be directly comparable to other studies in that we specifically excluded convulsive SE from our data. However, the important observation from these studies is that NCSE is common in comatose patients and that EEG monitoring should be considered an essential part of the coma evaluation.

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References


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