Prevalence of non-convulsive seizure and other electroencephalographic abnormalities in ED patients with altered mental status

Shahriar Zehtabchi, MD, Samah G. Abdel Baki, MD, Ahmet Omurtag, PhD, Richard Sinert, DO, Geetha Chari, MD, Shweta Malhotra, PhD, Jeremy Weedon, PhD, André A. Fenton, PhD, Arthur C. Grant, MD, PhD

Department of Emergency Medicine, State University of New York, Downstate Medical Center, Brooklyn, NY, USA

Bio-Signal Group Corporation, Brooklyn, NY, USA

Department of Neurology, State University of New York, Downstate Medical Center, Brooklyn, NY, USA

Scientific Computing Center, State University of New York, Downstate Medical Center, Brooklyn, NY, USA

Center for Neural Science, New York University, New York, NY, USA

Department of Physiology and Pharmacology, State University of New York, Downstate Medical Center, Brooklyn, NY, USA

Original Contribution

Prevalence of non-convulsive seizure and other electroencephalographic abnormalities in ED patients with altered mental status

Shahriar Zehtabchi, MD, Samah G. Abdel Baki, MD, Ahmet Omurtag, PhD, Richard Sinert, DO, Geetha Chari, MD, Shweta Malhotra, PhD, Jeremy Weedon, PhD, André A. Fenton, PhD, Arthur C. Grant, MD, PhD

Article history:
Received 23 June 2013
Accepted 3 August 2013


Contents lists available at ScienceDirect
American Journal of Emergency Medicine
journal homepage: www.elsevier.com/locate/ajem

A R T I C L E   I N F O

Article history:
Received 23 June 2013
Accepted 3 August 2013

A B S T R A C T

Prevalence of non-convulsive seizure and other electroencephalographic abnormalities in ED patients with altered mental status. Four to ten percent of patients evaluated in emergency departments (ED) present with altered mental status (AMS). The prevalence of non-convulsive seizure (NCS) and other electroencephalographic (EEG) abnormalities in this population is unknown. Objectives: To identify the prevalence of NCS and other EEG abnormalities in ED patients with AMS. Methods: A prospective observational study at 2 urban ED. Inclusion: patients ≥13 years old with AMS. Exclusion: An easily correctable cause of AMS (e.g. hypoglycemia). A 30-minute standard 21-electrode EEG was performed on each subject upon presentation. Outcome: prevalence of EEG abnormalities interpreted by a board-certified epileptologist. EEGs were later reviewed by 2 blinded epileptologists. Inter-rater agreement (IRA) of the blinded EEG interpretations was summarized with κ. A multiple logistic regression model was constructed to identify variables that could predict the outcome. Results: Two hundred fifty-nine patients were enrolled (median age: 60, 54% female). Overall, 202/259 of EEGs were interpreted as abnormal (78%, 95% confidence interval [CI], 73-83%). The most common abnormality was background slowing (58%, 95% CI, 52-68%) indicating underlying encephalopathy. NCS (including non-convulsive status epilepticus [NCSE]) was detected in 5% (95% CI, 3-8%) of patients. The regression analysis predicting EEG abnormality showed a highly significant effect of age (P < .001, adjusted odds ratio 1.66 [95% CI, 1.36-2.02] per 10-year age increment). IRA for EEG interpretations was modest (κ: 0.45, 95% CI, 0.36-0.54). Conclusions: The prevalence of EEG abnormalities in ED patients with undifferentiated AMS is significant. ED physicians should consider EEG in the evaluation of patients with AMS and a high suspicion of NCS/NCSE.

© 2013 Elsevier Inc. All rights reserved.

1. Introduction

Altered mental status (AMS), a nonspecific manifestation of brain dysfunction, is a common presentation in the emergency department (ED) [1]. This entity presents a unique diagnostic challenge, since obtaining an in-depth medical history or performing a thorough neurological examination is often difficult [2]. This leads to increased reliance on diagnostic tests to identify and properly treat the underlying cause of AMS. While imaging studies such as computed tomography (CT) or magnetic resonance imaging provide anatomical data, electroencephalography (EEG) is the only readily available test that provides information about the functional status of the brain.

EEG can increase or decrease the probability of specific AMS etiologies including toxic-metabolic encephalopathy, hepatic or uremic encephalopathy, herpes encephalitis, and various types of status epilepticus including absence status, complex-partial status, and
prolonged generalized convulsive status [3]. In addition, EEG can differentiate psychogenic from organic etiologies of AMS, and aid in determining whether the pathology is focal or diffuse [4].

The cause of AMS in up to 30% of patients is a neurological disorder [1]. Among these etiologies, prolonged generalized status epilepticus after the cessation of clinically evident seizures (generalized non-convulsive status epilepticus [NCSE]) is associated with significant morbidity and mortality if not diagnosed and treated early [5]. Despite this fact, a significant proportion of NCSE cases are diagnosed only after hospital admission, most commonly in the intensive care unit (ICU) [6]. This delay has been attributed to the hurdles associated with use of EEG in the ED (space limitations, personnel shortage, expertise requirement, etc.) and the absence of adequate index of suspicion among treating clinicians [3].

Previous studies have failed to produce an accurate estimate of the prevalence of NCS/NCSE in patients with AMS because of non-ED settings, small sample sizes, and other methodological limitations, including that it is difficult to obtain an EEG from patients in the ED, where the procedure is only rarely performed [7]. The prevalence of NCSE reported in these studies ranges from 8% to 30% [4,8–12].

Whether the use of EEG should be encouraged for ED patients with AMS requires that the scope of the problem (prevalence of EEG abnormalities including NCS and NCSE) is accurately assessed. If the estimate of EEG abnormalities proves substantial and clinically compelling, then it will have quantified an addressable unmet medical need. It may also lead to cost-benefit analyses to determine whether EEG should become standard of care for ED patients with AMS. Therefore, we conducted this study to estimate the prevalence of EEG abnormalities (including NCS and NCSE) in ED patients with AMS.

2. Methods

2.1. Study design

We conducted this prospective observational study at 2 urban academic centers. The study was approved by the joint institutional review board. The institutional review board waived the requirement for patient consent. However, a surrogate written consent was obtained when a legally authorized representative was available. The study was registered on a clinical trial registration website (Clinical-Trials.gov, #NCT01355211).

2.2. Study setting and population

The study was conducted at Kings County Hospital Center and SUNY Downstate Medical Center with annual ED census of 120000 and 75000, respectively.

Inclusion criteria: ED patients ≥13 years old with AMS. AMS was defined as any alteration in level of responsiveness or alertness or arousability and could present as lethargy, delirium, confusion, agitation, coma, disinhibition, labile/blunted affects, or unexpected psychosis.

Exclusion criteria: (1) Patients with an immediately correctable cause of AMS including a finger stick or serum glucose less than 60 mg/dL, hypothermia (body temperature below 35.0°C [95.0°F]), hyperthermia, heat exhaustion or heat stroke, or opioid overdose responding to naloxone. (2) Patients who were unable to undergo EEG recordings (e.g., severe scalp injury). (3) Hemodynamically unstable patients (SBP <90 mmHg). (4) Uncooperative or combative patients.

Patients who had an overt seizure in the ED were only included if they experienced a prolonged post-ictal period (at the discretion of the ED attending).

2.3. Study protocol

A convenience sample of ED patients with AMS was enrolled in the study. When a patient with AMS was identified, the patient was first evaluated by the ED attending (Fig.). If there was no immediately correctable cause of AMS (e.g., hypoglycemia), the ED attending notified one of the study investigators using a designated hotline (available 24 hours a day, 7 days a week). When the investigator on-call confirmed the eligibility of the patient, the on-call EEG technician was notified and started the enrollment process within 30-minutes. The EEG technicians were recruited and trained specifically for this study. A 30-minute EEG (21 EEG channels and one EKG channel) was obtained for each patient using a commercially available EEG device (Nicolet Monitor, Viasys, San Carlos, CA) with standard 9-mm gold-plated cup electrodes placed according to the international 10–20 system. When the recording was completed, the EEG was transferred to a secure hospital server for review by an epileptologist who reported the EEG findings to the ED attending within one hour. At a later time, each EEG recording was reviewed by 2 board-certified epileptologists who were unaware of clinical history, medications, treatment in the ED, and EEG technologists’ notes.

A Data Safety and Monitoring Board consisting of 3 members (an emergency medicine physician, a neurologist, as well as the study statistical consultant) reviewed the collected data at mid point (n = 130) and ensured adherence to the study protocols and checked for any patient safety concerns or issues.

2.4. Outcome measures

The goal of this study was to estimate the prevalence of NCS (including NCSE) and other EEG abnormalities. NCS was determined as the presence of a diffuse or generalized ictal electrographic pattern in an unresponsive patient without clonic, tonic or other convulsive
motor activity. NCSE was defined as either more than 10 minutes of continuous electrographic seizure activity or 2 or more electrographic seizures without normal EEG patterns between seizures.

2.5. Data analysis

Continuous variables are presented as medians and quartiles (25%, 75%). Rates are presented as percentages with 95% confidence intervals (CI). EEG interpretations made by the on-call epileptologist were used to calculate the prevalence of EEG abnormalities, reporting the following categories: Normal, status epilepticus, seizure, interictal epileptiform discharges with or without slowing, Burst suppression, and Uninterpretable. All EEGs interpreted as NCSE, NCS or burst-suppression were verified by a senior epileptologist (ACG). Disagreements were resolved by consensus.

Multiple logistic regression analysis was used to predict any EEG abnormality vs. normal result, after exclusion of the uninterpretable studies. Predictor variables included were age, gender, presence of acute head injury, history of seizures, seizure activity in the field, seizure activity in the ED, administration of anticonvulsant medications in the ED, administration of anticonvulsant medications in the field, abnormal neurological examination, and acute abnormal findings on head CT. Each of these predictors was dichotomous except for age, which was applied as a linear predictor. A logit link function was used, but instead of the usual complete-case logistic regression, the method of weighted EM was used [13]. This method allows all available data on all cases to be included. The software used for this analysis was LogXact PROC XMIXS (Cytel Corp., Cambridge, MA, USA); for other analyses SAS Release 9.2 (SAS Institute, Cary, NC) was used.

We also performed a supplementary analysis to compare four selected predictor variables (seizure in the field, seizure in the ED, anticonvulsant medications in the field, and anticonvulsant medications in the ED) between patients with status epilepticus (ie, burst-suppression or NCSE) or electrographic seizure (ie, NCS) compared to all other EEG findings. For this analysis, Fisher’s Exact test was used to test the association of predictors. Because of the small sample size (total number of patients with NCS/NCSE/BS: 18) multiple regression analysis was not attempted.

Inter-rater agreement was calculated using the 2 separate blinded interpretations of each EEG. Unweighted Cohen’s κ was used to measure inter-rater agreement.

Sample size analysis: We calculated that approximately 260 patients would be required to reach a projected 80% rate of EEG abnormality [14] with 95% confidence interval of 75% to 85% (2-tailed).

3. Results

During the study period, a total of 302 patients were screened and 261 patients were enrolled (41 did not meet inclusion criteria or violated the exclusion criteria). Two patients were excluded after enrollment (one for persistent hypotension and one for hypoglycemia). Eleven patients had more than one visit to the ED with AMS and were enrolled twice. The analyses were performed on 259 patients. The characteristics of the enrolled subjects are listed in Table 1.

Eighty eight percent of patients (n = 234) underwent a non-contrast head CT. Acute head CT findings were reported in 20% (95% CI, 15%-26%) of these patients.

Overall, 202/259 EEGs were interpreted as abnormal (78%, 95% CI, 73%-83%). The list of EEG interpretations is presented in Table 2. The subjects with a burst-suppression EEG pattern were being treated with propofol during the EEG recording. Five of these subjects had been diagnosed clinically with convulsive status epilepticus and one was treated with propofol for indications other than seizures. Among patients with NCS/NCSE, 8/12 (67%, 95% CI, 39%-86%) had previous history of seizure. The association of each independent variable with EEG finding is presented in Table 3.

The regression analysis predicting EEG abnormality showed a highly significant effect of age (P < .001), with adjusted odds ratio 1.66 (95% CI, 1.36-2.02) per 10-year age increment, suggesting that the odds of having an EEG abnormality in an AMS patient increases by 36%-102% per decade. No other predictor reached statistical significance (P < .05).

Our supplementary analysis revealed that anticonvulsant medication (ie, benzodiazepines) in the field (74% [95% CI, 51%-86%] vs 26% [95% CI, 11%-49%]), seizure in the field (86% [95% CI, 77%-92%] vs. 14% [95% CI, 8%-23%]), and seizure in the ED (87% [95% CI, 76%-93%] vs. 13% [95% CI, 7%-24%]) were significantly associated with NCE/NCSE/BS (P = 0.006, 0.008, and 0.045, respectively).

Table 1

<table>
<thead>
<tr>
<th>Characteristics of the enrolled patients (n=259)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Female gender</td>
</tr>
<tr>
<td>Presenting Symptom</td>
</tr>
<tr>
<td>Confusion</td>
</tr>
<tr>
<td>Lethargy</td>
</tr>
<tr>
<td>Coma/unresponsive</td>
</tr>
<tr>
<td>Agitation</td>
</tr>
<tr>
<td>Delirium</td>
</tr>
<tr>
<td>Unexpected Psychosis</td>
</tr>
<tr>
<td>Acute Head Injury</td>
</tr>
<tr>
<td>History of seizure</td>
</tr>
<tr>
<td>Seizure activity in the field</td>
</tr>
<tr>
<td>Seizure activity in the ED</td>
</tr>
<tr>
<td>Anticonvulsant medication in the field</td>
</tr>
<tr>
<td>Anticonvulsant medication in the ED</td>
</tr>
<tr>
<td>Abnormal neurological examination (other than AMI)</td>
</tr>
<tr>
<td>Acute head CT findings</td>
</tr>
<tr>
<td>Hospital admission (overall)</td>
</tr>
<tr>
<td>ICU admission</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>EEG interpretations in the enrolled subjects (emergency department patients with altered mental status)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
</tr>
<tr>
<td>EEG findings</td>
</tr>
<tr>
<td>Non-convulsive seizure activity</td>
</tr>
<tr>
<td>Non-convulsive status epileptic</td>
</tr>
<tr>
<td>Non-convulsive seizure without status</td>
</tr>
<tr>
<td>Burst suppression†</td>
</tr>
<tr>
<td>Interictal epileptiform discharges (with or without slowing)</td>
</tr>
<tr>
<td>Slowing only (including triphasic waves)</td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Uninterpretable</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval; ED, emergency department; CT, computerized tomography scan; ICU, intensive care unit.

* Due to treatment with propofol.
Our multiple logistic regression analysis revealed that age is a predictor of EEG abnormality in ED patients with AMS. Every decade increase in age is associated with a significant increase (36 to 102%) in odds of having an abnormal EEG. Our supplementary analysis also showed that patients who have seizure in the field or in the ED and those who receive anticonvulsant medications (e.g., benzodiazepines) in the field are at higher risk of EEG diagnosis of seizure in the ED, although the precision of these results is limited by the small number of NCS/NCSE/BS cases (n = 18) in this supplementary analysis. These findings suggest that ED physicians should consider EEG in the evaluation of AMS patients at risk for NCS/NCSE, since these entities can only be diagnosed with EEG.

Over half of patients with NCSE are diagnosed more than 24 hours after ED arrival [6]. This delay has profound clinical consequences, as the duration of NCSE has been associated with high mortality (up to 50%) [5, 6, 16], and can exacerbate a preexisting brain injury [17–19]. Only 20% of patients who survive NCSE regain full neurological function [5, 16, 20].

The 5% prevalence of NCS/NCSE in this study is lower than the 8–30% range reported in prior publications. In our study, 259 patients with AMS meeting pre-defined inclusion and exclusion criteria were enrolled prospectively. In addition, the EEGs were recorded for 30 minutes with a full set of “10-20 system” electrodes, as soon as possible after enrollment (median 79 minutes). Therefore, our estimate of 5% NCS/NCSE in ED patients with undifferentiated AMS is derived from a methodologically rigorous approach. Prior studies reporting the prevalence of NCS/NCSE in ED patients were often designed such that the pre-test probability of NCS/NCSE was relatively high. For instance, some studies only enrolled patients admitted to the hospital, or those who underwent continuous EEG monitoring [4, 8–12, 21]. In addition, patients whose cause of AMS remains unknown after an initial diagnostic evaluation, also have an

Eighty-seven percent (n = 226) of the EEGs were reviewed by 2 epileptologists blinded to the clinical information as previously described. Kappa representing agreement of epileptologists in blinded interpretation of EEGs was 0.45 (95% CI, 0.36–0.54).

### 4. Discussion

According to this study, 78% (95% CI, 73%-83%) of ED patients with AMS have some form of EEG abnormality with 58% demonstrating slowing in the absence of other pathologic findings. Although slowing is a non-specific manifestation of cerebral dysfunction, its magnitude correlates with the functional severity of a clinical encephalopathy, and its distribution can help distinguish between diffuse, focal, or multi-focal pathologies. For instance, while transient diffuse slowing is a common finding after concussion, focal slowing after head injury indicates cerebral contusion even in the absence of focal deficits on neurological examination or focal abnormalities on head CT scan [15].

Seven EEGs contained continuous triphasic waves, an EEG pattern indicating severe encephalopathy of metabolic origin, usually hepatic or renal failure [15]. Normal EEGs, present in 20% of enrolled patients, are particularly helpful in distinguishing organic from psychiatric causes of AMS. If available early in the patient’s ED evaluation, this result may prevent additional unnecessary tests and expedite referral to an appropriate specialist. However, the real impact of the abnormal EEG findings on clinical outcomes (e.g. mortality) needs to be assessed in a large randomized controlled trial.

This study also revealed that 5% (95% CI, 3%-8%) of ED patients with AMS present with NCS (including NCSE). In the ED setting, these electrographic findings usually imply prolonged convulsive status epilepticus and these patients should be treated emergently.

### Table 3
Comparison of variables in different EEG categories

<table>
<thead>
<tr>
<th>Variables</th>
<th>EEG categories (n, %, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NCS/NCSE (n = 12)</td>
</tr>
<tr>
<td>Age *</td>
<td>64 (50-79)</td>
</tr>
<tr>
<td>Gender (Female)</td>
<td>8/12</td>
</tr>
<tr>
<td>Acute Head Injury</td>
<td>67%</td>
</tr>
<tr>
<td>History of seizure</td>
<td>8/12</td>
</tr>
<tr>
<td>Seizure activity in the field</td>
<td>67%</td>
</tr>
<tr>
<td>Seizure activity in the ED</td>
<td>64%</td>
</tr>
<tr>
<td>Anticonvulsive medication in the field</td>
<td>4/12</td>
</tr>
<tr>
<td>Anticonvulsive medication in the ED</td>
<td>33%</td>
</tr>
<tr>
<td>Neurological findingsb</td>
<td>3/12</td>
</tr>
<tr>
<td>Acute head CT findings</td>
<td>25%</td>
</tr>
</tbody>
</table>

* Median and quartiles (25%, 75%).

* Other than AMS.

* With or without slowing.
increased pre-test probability for NCS, since many other causes of AMS have been excluded.

Privitera et al. [11] enrolled 192 patients with AMS who had an EEG ordered in the ED, ICU or regular wards, of whom approximately 29% were diagnosed with NCS. [11] In another study, Kapadia et al. [10] enrolled 70 ICU patients at risk of NCSE (AMS with history of epilepsy) in a tertiary care center, and detected NCS in 10%. [10] Bautista et al. [8] performed a 5-minute abbreviated EEG on 25 ED patients with AMS and diagnosed NCS in 2 patients (8%). Other studies have produced results that fall within this range (8-30%) [4,9–12,21].

Despite its potential value in the diagnosis and treatment of ED patients with AMS, EEG remains a difficult test to obtain in the ED. Incorporating EEG into the evaluation of ED patients with AMS requires 24/7 availability of EEG technologists and neurologists. Recording an EEG in an ED is also often complicated by space limitations, time limitations, and the electrically hostile environment resulting from cardiac monitors, infusion pumps, ventilators, and so on. The investigators are currently assessing the diagnostic accuracy of a miniature wireless EEG device (Bio-Signal microEEG) for ED patients with AMS. The ED-friendly characteristics of this device may facilitate the use of EEG in the emergency departments by overcoming some of the hurdles associated with the use of EEG in the ED. However, whether the use of EEG should be encouraged for ED patients ultimately depends upon evidence that its use improves patient outcomes in a cost-effective manner.

5. Limitations

Due to the small number of NCS and NCSE cases, we were not able to perform a regression analysis to identify factors that could directly predict these particular outcomes. Instead, we used any EEG abnormality as the dependent factor for performing this analysis.

Approximately 65% of patients enrolled in our study received anticonvulsant medications in the ED (mostly benzodiazepines). We did not distinguish between those who received benzodiazepines for seizure or for other indications (e.g. agitation).

The inter-rater reliability for the blinded EEG interpreters in this study was low. This issue has been extensively discussed in the literature [22,23]. However, for reporting the prevalence of EEG abnormalities we relied on interpretations made in the usual manner by reviewers with knowledge of patient history, medications, and EEG technologist comments. In addition, all NCS/NCSE and burst-suppression EEGs were independently reviewed by one of the authors (ACG).

This study was conducted in 2 urban academic institutions serving a culturally and ethnically diverse population of low socioeconomic status. The findings of the study may not be generalizable to other populations.

Lastly, the enrollment occurred 24/7 and the ED physicians referred subjects for enrollment by calling the study hotline. In addition, the study coordinators screened the emergency departments several times a day to identify potential candidates. However, it is possible that some of AMS patients were not referred for enrollment; subjecting the study to a sampling bias. It is also likely that ED staff referred patients with higher pre-test probability of NCS/NCSE for enrollment. Because of the broad spectrum of AMS presentations, we were not able to estimate the total number of AMS patients that visited our EDs during the study period.

6. Conclusion

The prevalence of NCS (5%) and overall EEG abnormalities (78%) in ED patients with undifferentiated AMS is significant. ED physicians should have a low threshold for ordering EEG for evaluation of patients with AMS especially those with higher suspicion of NCS/NCSE.

Acknowledgments

The authors appreciate the assistance and support of the following individuals without whom, conducting this study would not have been possible: Ewa Koziołynska, Douglas Maus, Tresa McSween, Katherine Mortati, Alexandra Reznikov, Helen Valsamis, Roger Cracco, Sage Wiener, Vanessa Arnedo, John Gridley, and Krishnakant Nammi.

References