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Non-convulsive Seizure in Patients Presenting with Altered Mental Status: An Evidence-based Review

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Abstract

Definitive diagnosis of non-convulsive seizure (NCS) can be made only by EEG, and delay in diagnosis can increase morbidity, resource utilization, and length of hospitalization. We performed an evidence-based literature review to estimate the prevalence of NCS in patients with altered mental status (AMS) of unknown cause. PUBMED, EMBASE, the Cochrane Library and other resources were searched for studies that included AMS and seizure as topics. The resulting 276 articles were screened for predetermined inclusion and exclusion criteria, leaving five studies enrolling 478 patients for review. The prevalence of NCS in AMS patients ranged from 8% to 30% (overall prevalence of 21.5%; 95% CI, 18%–25%), suggesting that the prevalence of NCS is sufficiently high to consider routine use of urgent EEG in such patients. However, methodological weaknesses limit the generalizability of the results. A large, prospective study enrolling and screening for NCS all patients who present with acute AMS is needed.

Keywords

Non-convulsive seizure; Altered mental status; EEG; Evidence-based medicine; Literature review; Seizure; Status epilepticus

Introduction

Two to ten percent of all patients presenting to emergency departments (ED) in the US present with altered mental status (AMS). [1] The underlying cause can usually be identified quickly and appropriate treatment initiated in those with hypothermia, hypoglycemia, alcohol or drug intoxication, or cardiopulmonary compromise. Some of the remaining patients will have non-convulsive seizure (NCS) or non-convulsive status epilepticus (NCSE), diagnoses that, if made quickly, will precipitate appropriate acute management, reduce unnecessary diagnostic procedures and length of hospitalization, and reduce morbidity. [2–5]

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The prevalence of NCS/NCSE in patients presenting with AMS is unknown. The absence of large, prospective studies addressing this issue results in part from the limited availability of electroencephalography (EEG) in EDs in particular, and in hospitals on a 24/7 basis in general. EEG is the only test that definitively establishes the diagnosis of NCS when clinical signs of seizure are absent. [6] Because EEG is required to make the correct diagnosis, many investigators believe that NCS is an under-diagnosed and under-reported entity in patients with acute AMS. [7–9] Physicians caring for such patients, particularly in the ED but also in a hospital ward or ICU, may underestimate the risk of NCS and therefore delay or not consider ordering an EEG. Without EEG, the NCS may go unrecognized and thus perpetuate the misconception that AMS is rarely due to NCS.

With two goals in mind, we performed a critical evidence-based literature review on NCS in patients presenting with AMS. First, we wanted to estimate the prevalence of NCS in such patients, using best available data. Second, we sought to evaluate potential weaknesses in study methodologies, and thereby formulate a study design that would overcome these limitations and provide more definitive information on the prevalence and risks for NCS in patients with acute onset AMS.

Criteria For Considering Studies For The Review

We considered observational cohort studies (prospective or retrospective) as the target study design for this review. We used a widely accepted definition of NCS pertinent to this study, namely a seizure causing AMS without clonic, tonic or other convulsive motor activity, confirmed by the presence of at least one electrographic seizure lasting more than 10 seconds. Non-convulsive status epilepticus was defined as NCS and either EEG evidence of continuous or nearly continuous seizures for more than 10 minutes, or presence of two or more sequential electrographic seizures without complete recovery of consciousness in between seizures. [10] In this review, the term NCS refers to both focal and generalized NCS as well as NCSE.

Studies were selected for review if the primary presenting complaint was AMS, and NCS was confirmed by EEG. There was no restriction on subject age. Our initial intent was to include only those studies that performed the EEG within a few hours of patient presentation, but only one study met that criterion. [11] Thus, we decided to include studies in which the EEG was performed within 24 hours of presentation. The EEG was not limited to any particular technical variation based on type or number of electrodes used, or to a minimum duration. However, the EEG had to be interpreted by a trained neurologist or electroencephalographer. We planned to examine the prevalence of NCS in two subgroups: adult and pediatric patients, and those with or without a history of epilepsy.

Search Methods

We searched the MEDLINE database from 1966 to December 2010 and EMBASE from 1980 to December 2010. We also scanned the databases of the Cochrane Library through December 2010, [12] Emergency Medical Abstracts from 1977 through December 2010, [13] and other online resources including BestBETS. [14] Bibliographies of eligible studies were reviewed for citations of additional relevant studies. The MEDLINE search strategy is presented in the appendix.

The search yielded 276 studies, which were evaluated according to the algorithm given in Figure 1. If a study enrolled a mix of patients with or without AMS, we sought the number of NCS cases in those patients with AMS, if such information was provided in the article. If it was not, we contacted the authors to obtain the data. Similarly, if the door-to-EEG time was not mentioned in the publication, the authors were contacted to provide this

information. After applying the inclusion/exclusion criteria and collecting the necessary information from the authors, five studies remained suitable for review. [11, 15, 16, 17, 18] The literature search did not reveal any systematic review or meta-analysis on this topic.

Description Of The Included Studies

A description of the five studies is provided in Table 1. The trials enrolled 478 patients and were all published in English. Two studies were conducted in the United States, [11,18] one in Canada, [15], one in India, [17], and one in France. [16] The Canadian study was restricted to pediatric patients, [15] while the other four [11,16,17,18] included patients of various age groups ranging from 1 day to 93 years. The trials were different with regards to the medical setting; two of the trials were conducted in the ICU, [15,17] one trial took place in the ED, [11] and two enrolled patients in the ED, hospital ward and ICU. [16,18]

Bautista et al. used an abbreviated 5 minute, 16 channel EEG. [11] The other studies performed a standard EEG with at least 18 electrodes lasting at least 20 minutes. In the study by Kapadia et al, EEGs were interpreted by a board certified neurologist. [17] In the other four studies EEGs were interpreted by certified electroencephalographers. [11,15,16,18] Electrographic criteria for NCS and NCSE were the same for all trials except for the one by Bautista et al. [11] Those authors defined NCSE as altered sensorium associated with 5 minutes of electrographic seizure activity, since they recorded only 5 minutes of EEG rather than the usual 20–30 minutes.

Quality Assessment Of The Included Studies

Several quality assessment scales targeting observational studies have been developed, but none of them has been fully validated. Additionally, research has shown that quality scores (numeric scores based on weights given to each item in a scale) are arbitrary, unreliable, and hard to interpret. [19] Therefore, we decided not to use quality scores and rather to perform the quality assessment using a simple checklist (Table 2). All studies were assessed separately by two of the authors and a third author reviewed the results for consistency and accuracy.

We chose a selection of quality assessment criteria proposed by the following sources based on their suitability for the objectives of this review: 1. The “Newcastle-Ottawa Scale for assessing the quality of non-randomized studies in meta-analyses” (recommended by the Cochrane Non-Randomized Studies Methods Working Group), [20] 2. “Systems to Rate the Strength of Scientific Evidence” published by the Agency for Healthcare Research and Quality (AHRQ), [21] and 3. User’s guide to medical literature. [22] These sources recommend assessing the quality of observational studies by criteria that fall into three major categories: selection of cohorts, comparability of cohorts (not relevant to this review), and methods of outcome ascertainment. [20–22]

With respect to the data sought in this review, i.e. the prevalence of NCS in patients presenting with AMS, each of the studies has significant methodological weaknesses. Only one study enrolled *consecutive* patients presenting (to the ED) with AMS whose cause could not be quickly determined. [11] This is also the only study wherein the EEG was performed within one hour of presentation. However, only 25 patients were enrolled and the EEG duration was only five minutes. One study enrolled consecutive patients for whom an EEG was ordered *due to suspicion of NCS*, but not all patients had AMS (our analysis included only those patients who did have AMS). [16] This sampling method may have missed some patients with AMS due to NCS. The other 3 studies did not mention their sampling method. [15, 17, 18]

Another limitation of all five studies is inadequacy of case validation, i.e. validating NCS. Only two studies independently validated their cases by one or more blinded assessors. [11, 15] None of the studies measured inter-rater variability for the abstracted data or for the EEG interpretations. Additionally, all of the trials are vulnerable to various sampling biases (e.g. selection and spectrum bias) since all but one enrolled subjects with a relatively high pre-test probability for NCS, and did not enroll consecutive patients with AMS. [11] Lastly, the study by Saengpatrachai et al. was a retrospective chart review, which subjects its results to the biases and limitations inherent to such study designs. [15]

Results

Of the 478 subjects with AMS enrolled in the five studies, the mean prevalence of NCS was 21.5% (95% CI, 18% to 25%). In the one study that enrolled only children, the prevalence was 16.3% (95% CI, 11.1% to 23%). A history of epilepsy was associated with an increased risk of NCS in the one trial that provided the data required for this analysis (relative risk: 1.8, 95% confidence interval, 1.0 to 3.2, $p=0.04$). [16] The rate of NCS in each of the trials is summarized in figure 2. The prevalence of NCS in the one study that enrolled consecutive ED patients with AMS was only 8%, but this is the study with a sample size of 25 and a 5 minute EEG. [11]

In addition to cases meeting definitive EEG criteria for NCS, Privitera et al. also considered subjects with equivocal EEG findings that responded to benzodiazepines (i.e. alteration or interruption of the EEG abnormality) to have NCS. [18] Since this approach is controversial, and non-seizure EEG patterns may respond to benzodiazepine administration, we excluded these uncertain cases from our analysis and calculated NCS prevalence only in patients with definitive EEG criteria for NCS.

Discussion

Despite their limitations, the included studies demonstrate that NCS is not rare in patients with acute AMS, whose cause cannot be quickly identified. Three studies not included in this review due to violation of inclusion/exclusion criteria reported a prevalence of electrographic seizure comparable to that in the included studies. [23–25] Classen et al detected NCS in 17% of 575 in-patients who underwent continuous EEG monitoring. [23] Young and Doig recorded electrographic seizures in 20% of 55 patients in coma, 24 – 72 hours after coma onset [24], and Towne et al reported an 8% rate of NCSE in 236 patients with coma and no clinical signs of seizure who underwent EEG within 3 days of coma onset. [25] The latter two studies illustrate the crucial importance of diagnostic EEG in patients with the most extreme form of AMS of unknown etiology, i.e. coma.

The reviewed studies also reveal that AMS due to NCS is common in children, where the diagnosis of NCS is especially challenging because changes of behavior, responsiveness and even consciousness may not be taken as seriously or recognized as quickly as in adults. Consistent with this finding, recent epidemiological studies have recommended prolonged EEG monitoring to exclude NCS in children with unexplained altered consciousness or after brief isolated convulsions, as the majority of children diagnosed with NCS had preceding clinical seizures. [26,27]

Since most patients presenting with AMS are initially evaluated in an ED, it is particularly important that ED physicians and their neurology consultants appreciate the risk of NCS in such patients, and have a correspondingly low threshold for obtaining an urgent EEG. Unfortunately, urgent EEG is often not available in ED or hospital wards on a 24/7 basis, and thus the diagnosis may be missed or delayed. Several studies have reported significant

delays in diagnosing NCS, especially when AMS was initially attributed to another etiology such as psychiatric illness, toxic or metabolic encephalopathy or infection. [2,28] Delay in identifying NCS has been associated with increased morbidity, mortality, length of hospital stay, and cost of care in ICU settings. [2–5, 29]

The apparent prevalence of NCS in patients presenting with AMS, combined with the risks of delayed diagnosis support the argument that urgent EEG with rapid interpretation should be available in ED at all times. If EEG were included among the initial diagnostic tests in AMS patients, it would be possible to either rule out NCS and focus on other potentially serious pathologies, or rule in NCS and immediately begin appropriate treatment. In fact, Khan et al showed that EEGs performed on an acute, non-elective basis for an emergency indication could significantly impact clinical management in selected clinical situations commonly encountered in ED, including AMS. [30]

Contemporary, portable, digital EEG acquisition units have simplified the physical logistics of obtaining EEGs on ED patients. Similarly, commercially available EEG equipment allows for remote, real-time interpretation using the internet, a process analogous to virtual radiology, which is common practice in many EDs. However, 24/7 availability of EEG technologists and electroencephalographers remains a logistical and financial challenge. It is possible that cost savings obtained from quickly ruling NCS/NCSE in or out of the differential diagnosis would offset the additional costs of 24/7 EEG acquisition and interpretation, but this has not been studied.

As mentioned previously, none of the reviewed studies, let alone the remaining 271 relevant articles not meeting the inclusion criteria, adequately answers what seems like a simple question: what is the prevalence of NCS in patients presenting with acute AMS whose cause cannot be quickly determined? With respect to this question, weaknesses of the five studies can be summarized as follows: not enrolling consecutive patients with AMS, small sample size, delay in obtaining EEG, limited EEG duration, and inadequacy of case validation.

Thus, a definitive study to determine the prevalence and risks for NCS in AMS patients should be adequately powered, prospectively enroll consecutive patients presenting with AMS, obtain a standard EEG (full complement of 10–20 system electrodes lasting at least 20 minutes) shortly after presentation (preferably within an hour), and include methods to validate cases with particular attention to inter-rater reliability of EEG interpretation. In the meantime, the available data suggest that the prevalence of NCS in patients with acute AMS whose cause cannot be quickly determined is at least 8% and may be as high as 30%. Until more reliable data are available, physicians evaluating such patients should maintain a high index of suspicion for NCS and have a correspondingly low threshold for obtaining a diagnostic EEG study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

evidence-based literature review to estimate prevalence of NCS in patients with AMS

Five studies enrolling 478 patients were reviewed

Prevalence of NCS in AMS patients ranged from 8% to 30% (overall prevalence 21.5%)

Each of the five studies had significant methodological weaknesses

A prospective study is needed to determine the prevalence of NCS in AMS patients

Figure 1.
The Process of selecting studies suitable for inclusion in the final review.

Figure 2. Forest plot representing the prevalence of nonconvulsive seizure in the included trials
 For each trial, the box corresponds to the observed prevalence of nonconvulsive seizure (NCS) and the horizontal line defines the 95% confidence interval. The size of the box reflects the number of patients enrolled in the respective trial.

Table 1

Description of the five reviewed studies.

Study	Population	Intervention	Outcome
Bautista et al, (2007)¹¹	<ul style="list-style-type: none"> Institution: A tertiary care university-based hospital in United States N: 25 ED patients. Age: Adults (age range: 15 to 91 yrs). Inclusion Criteria: ED patients with AMS of unknown cause. Exclusion Criteria: (1) findings in the initial history that already indicate the cause of AMS; (2) glucose level greater than 200mg/dl or less than 40mg/dl; (3) clinically unstable for EEG. 	<ul style="list-style-type: none"> Abbreviated EEG: A 5- minute, 16- channel EEG (AbEEG) performed in the ED, 20 minutes after recognition of AMS symptoms. A board-certified EEGer blinded to the clinical scenario reviewed the AbEEGs. Some patients received standard EEG at the discretion of ED physician 	<ul style="list-style-type: none"> EEG outcome: 1. NCS (electrographic evidence of seizure), 2. diffuse abnormalities without seizure, 3. focal abnormalities without seizure, 4. Normal, and 5. Uninterpretable. Cause of AMS determined from retrospective chart review: 1) NCSE, 2) focal brain abnormality without seizure, 3) diffuse encephalopathy or non-neurologic event without seizure, 4) psychogenic, 5) unknown
Praline et al, (2007)¹⁶	<ul style="list-style-type: none"> Institution: Single-center study in France N:111 hospitalized patients including ICU, ED, and regular wards. Age: Pediatric, (average age: 3.4 yrs $\pm$ 53.4 months) and Adults (average age:53 $\pm$ 17.2 yrs). Inclusion Criteria: Presence of a medical emergency deemed by the attending physician as requiring an emergent EEG for subsequent patient management, including ruling in or out NCS. Exclusion Criteria: EEGs requested for brain death and organ harvest. Note: Only 44 patients had AMS and were included in our analysis. 	<ul style="list-style-type: none"> EEG: $\geq$ 20-minutes, 20- channels within 24 hours of presentation. Eight electrodes were used when bedside recordings were performed. EEGs were performed within an hour after being requested. EEGs were interpreted by two certified EEGers and in case of disagreement both interpretations were sent to a third reviewer. 	<ul style="list-style-type: none"> NCSE (discrete electroencephalographic seizures, continuous spike and wave activity, or rhythmic recurrent epileptiform activity). Clinicians were surveyed about the impact of the EEG on the patient's management.
Saengpatrachai et al, (2006)¹⁵	<ul style="list-style-type: none"> Institution: Single-center study in Canada N: 141 patients. Age: Pediatrics: 1 month to 18 years Inclusion Criteria: patients admitted or transferred to the Pediatric ICU with decrease in the level of consciousness and no overt seizure activity. 	<ul style="list-style-type: none"> A 30-minute, "10–20" EEG performed within 24h of AMS onset. EEG recordings were blindly reviewed by at least two board certified EEGers. 	<ul style="list-style-type: none"> NCS, defined as at least one episode of focal or generalized repetitive rhythmic epileptiform discharges on EEG with changes in amplitude and frequency, with clear cut onset and offset and lasting longer than 10 seconds in duration.

Study	Population	Intervention	Outcome
	<ul style="list-style-type: none"> Exclusion Criteria: full-term newborns under 28 days of age. 		
Kapadia et al, (2005)¹⁷	<ul style="list-style-type: none"> Institution: A tertiary care center in India N: 70 ICU patients Age: 10–73 years. Inclusion Criteria: <ol style="list-style-type: none"> AMS unconscious patients at risk for NCSE (history of epilepsy); unconscious patients with subtle nystagmoid eye movements. 	<ul style="list-style-type: none"> Standard EEG EEGs performed with a mean interval of 13 hours from presentation. EEGs interpreted by board-certified neurologists 	NCSE, defined as either focal rhythmic or semi-rhythmic slow or sharp waves superimposed on a slow background.
Privitera et al, (1994)¹⁸	<ul style="list-style-type: none"> Institution: Single-center study in US. N: 192 hospitalized patients (wards, ICU, and ED), 198 EEGs Age: pediatric and adult. Mean and SD could not be determined from available data. Inclusion Criteria: Patients with AMS and EEG ordered for possible NCSE. 	<ul style="list-style-type: none"> An 18 or 21 channel EEG was performed on a 24/7 basis within 24 hours of presentation. Recordings were initially interpreted by a senior neurology resident, EEG fellow or staff EEGer, but all EEGs were ultimately reviewed by a board-certified EEGer. 	<ul style="list-style-type: none"> NCSE: discrete electrographic seizures or continuous spike-wave activity lasting ≥ 30 minutes, without return to normal level of consciousness between seizures.

Abbreviations: ED: Emergency Department; AMS: altered mental status; EEGer: electroencephalographer; NCS: Nonconvulsive seizure; NCSE: Nonconvulsive status epilepticus; ICU: intensive care unit

Table 2

Quality assessment of the reviewed studies.

	Bautista et al, 2007 ¹¹	Praline et al, 2007 ¹⁶	Saengpatrachai et al, 2006 ¹⁵	Kapadia et al, 2005 ¹⁷	Privitera et al, 1994 ¹⁸
Study design	Prospective observational	Prospective observational	Retrospective chart review	Prospective observational	Prospective observational
Inclusion criteria	Adequately described	Adequately described	Adequately described	Adequately described	Adequately described
Selection of participants	Continuous sampling@	Convenience sampling*	Not mentioned	Not mentioned	Not mentioned
Cohort representative of population at risk?	Yes	Yes	Yes	Yes	Yes
Method of outcome determination	EEG criteria	EEG criteria	EEG criteria	EEG criteria	EEG criteria
Independent blinded outcome validation	Yes	No	Yes	No	No
Inter-rater variability	Not measured	Not measured	Not measured	Not measured	Not measured
Method of quantifying uncertainty	Adequately described	Adequately described	Not described	Not described	Adequately described

@ This study enrolled consecutive patients with AMS of unknown cause.

* This study enrolled consecutive patients who underwent EEG to rule out nonconvulsive seizure. However, not all patients with altered mental status were enrolled.