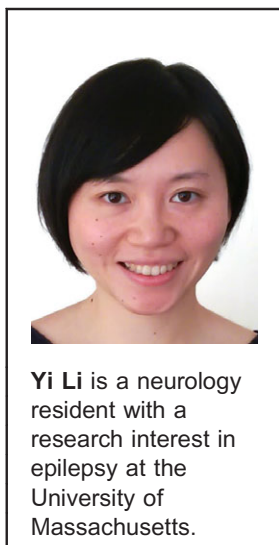




Anion gap can differentiate between psychogenic and epileptic seizures in the emergency setting

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SUMMARY

Differentiation between psychogenic nonepileptic seizures (PNES) and generalized convulsive epileptic seizures (ES) is important for appropriate triaging in the emergency department (ED). This can be difficult in the ED, as the event is often not witnessed by a medical professional. In the current study, we investigated whether anion gap (AG), bicarbonate, and the Denver Seizure Score (DSS) could differentiate between PNES and ES. Of a total of 1,354 subjects reviewed from a tertiary care medical center, 27 PNES and 27 ES patients were identified based on clinical description and subsequent electroencephalogram. Multivariate logistic regression analysis and receiver operating characteristic curves were used to determine whether there was an association between seizure type and AG, bicarbonate, or DSS (24-bicarbonate + 2 × [AG-12]) when samples were drawn within 24 h of the concerning event. The result showed that sensitivity and negative predictive value dropped markedly for all measures if samples were drawn >2 h after the event; the sensitivity was similar for AG and DSS and higher than for bicarbonate. We propose that AG > 10 (sensitivity of 81.8%, specificity of 100%) in the first 2 h after the event could be used as a potential tool in the ED to help differentiate between PNES and ES.

KEY WORDS: Acidosis, Seizure, Nonepileptic seizure, Anion gap, Denver Seizure Score.

Differentiation between psychogenic nonepileptic seizures (PNES) and generalized convulsive epileptic seizures (ES) is important for therapeutic decision making and appropriate triaging of patients in the emergency department (ED). This can be difficult in the ED, as the event concerning for seizure is often not witnessed by a medical professional and semiology descriptions from lay witnesses can be misleading. Video-electroencephalography (EEG) is the gold standard for diagnosis but is not readily available in most EDs.

Anion gap (AG) metabolic acidosis following ES has been previously observed.¹ Recently, the Denver Seizure Score (DSS) has been developed, as metabolic acidosis and bicarbonate level could help distinguish syncope from ES.²

However, it is unclear whether these measures can differentiate between ES and PNES. Here, we investigate whether AG, bicarbonate, or DSS can help differentiate between ES and PNES in the ED.

METHODS

We conducted a retrospective chart review on subjects who visited a single tertiary care medical center ED (University of Massachusetts Memorial Hospital, Worcester, MA, U.S.A.) between January 1, 2014 and June 30, 2016. Inclusion criteria were ED discharge diagnosis of “generalized seizures” or “generalized shaking episodes” for subjects older than 18 years, plus a well-documented spell onset within 24 h of a basic metabolic panel drawn in the ED. Subjects were excluded from the study if they had other documented active medical problems that could cause acidosis and confound the analysis, such as sepsis, alcohol, or medicine toxicity. Subjects on medications that could cause metabolic acidosis were excluded unless they had a baseline normal basic metabolic panel within the 12 weeks

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preceding their presentation on the same medications. Subjects were then split into ES and PNES groups. Subjects were included in the ES group if the documented semiology of their event was consistent with a generalized convulsive seizure and they had an abnormal interictal EEG showing epileptiform discharges. Subjects were included in the PNES group if they subsequently received video-EEG capturing their typical event and confirming PNES. Subjects were excluded if they did not meet these diagnostic criteria. This study was performed with approval and in accordance with the guidelines of the institutional review board (H00010215) at the University of Massachusetts Medical School.

AG was calculated as sodium – (chloride + bicarbonate). DSS was calculated as 24-bicarbonate + 2 × (AG-12). Continuous variables are reported as mean ± standard deviation. Categorical variables are reported as proportions. Between-group comparisons for continuous and ordinal variables were made with Mann–Whitney *U* test. Categorical variables were compared using the χ^2 test as appropriate. Multivariate logistic regression analysis and receiver operator characteristic curves were calculated using SPSS software v22.0 (IBM, Armonk, NY, U.S.A.).

RESULTS

Demographic data of patients in the ES and PNES groups

Among the total screened 1,354 patients, 126 subjects met inclusion criteria. Of these, 72 subjects were excluded because they had other medical conditions, toxicities, or chronic medications that could cause metabolic acidosis. Of the remaining 54 subjects, enough medical record information was available to stratify 27 to the ES group and 27 to the PNES group. Patients enrolled in the ES group had documented generalized rhythmic body jerking and cognitive impairment, often accompanied with fracture, urinary incontinence, or tongue bitten. The episodes usually lasted 1–3 min, and none of the episodes were longer than 5 min. All the patients recruited in the ES group did not have repetitive seizures that occurred within 6 h, to avoid the potential influence of the repetitive episodes on the study analysis. For the patients enrolled in the PNES group, their spells were often described with nonrhythmic general body shaking, side-to-side body shaking, vocalization during the tonic–clonic phase, et cetera. The spells usually lasted longer and had variable duration from 1 to 10 min, and there were usually two to six repetitive episodes upon the day of evaluation.

Dynamic evolution of acid-base equilibrium in the ES and PNES patients

As shown in Table S1, subjects were subgrouped based on the time between the event and the collection of blood to evaluate the effect of time on the ability of these values

to differentiate between ES and PNES. The AG was elevated and bicarbonate was lower in the ES group compared to the PNES group at all time periods after the event ($p < 0.05$). There was no significant difference between ES and PNES groups for chloride, potassium, or sodium ($p > 0.05$).

The DSS, which is calculated from AG and bicarbonate values, remained <0 within 24 h of the event in the PNES group. DSS was significantly higher in the ES group ($p < 0.05$) but decreased with time from the event.

Efficacy of utilizing bicarbonate, AG, and DSS to differentiate between PNES and ES

Multivariate logistic regression analysis was also used to model the association of bicarbonate, AG, and DSS when controlling for age and the time to sample collection as possible confounders. When controlling for these two confounding variables, AG (odds ratio [OR] = 1.733, 95% confidence interval [CI] = 1.24–2.42), bicarbonate (OR = 0.804, 95% CI = 0.66–0.97), and DSS (OR = 1.192, 95% CI = 1.07–1.33) remain associated with ES.

The receiver operating characteristic (ROC) curve for sensitivity and specificity of ES detection was plotted for bicarbonate, AG, and DSS. Areas under the ROC curve (AUCs) within 24 h were 0.678, 0.822, and 0.812, respectively ($p < 0.05$, Fig. 1). The AUC decreased as time progressed (Figs. 1 and 2).

Bicarbonate level < 20 , AG > 10 , and DSS ≥ 0 within 24 h following the event yielded 100% specificity and positive predictive value within our sample to identify ES. Using these cutoff values, both AG and DSS are more sensitive and have better negative predictive value (NPV) compared with bicarbonate value at all time points within the first 24 h after the event (Fig. 2). Both the NPV and sensitivity decreased for bicarbonate, AG, and DSS when samples were collected >2 h after the event.

DISCUSSION

We utilized routine laboratory values obtained in the ED to differentiate between ES and PNES. DSS showed no additional benefit over AG in our study, and bicarbonate level is less sensitive than both for ES. We propose that an AG > 10 in samples drawn within 2 h of the event (sensitivity of 81.8%, specificity of 100%, NPV of 84.6% for the diagnosis of ES vs. PNES) could help differentiate between ES and PNES in the ED.

AG is calculated as sodium – (chloride + bicarbonate). It is unclear by which exact mechanism that AG showed an additional benefit over bicarbonate in differentiating between ES and PNES, as sodium and chloride values were not significantly different between groups. However, there is a trend toward lower chloride values in ES compared to PNES (Table S1). A larger sample size may reveal a significant difference between groups in chloride values and more

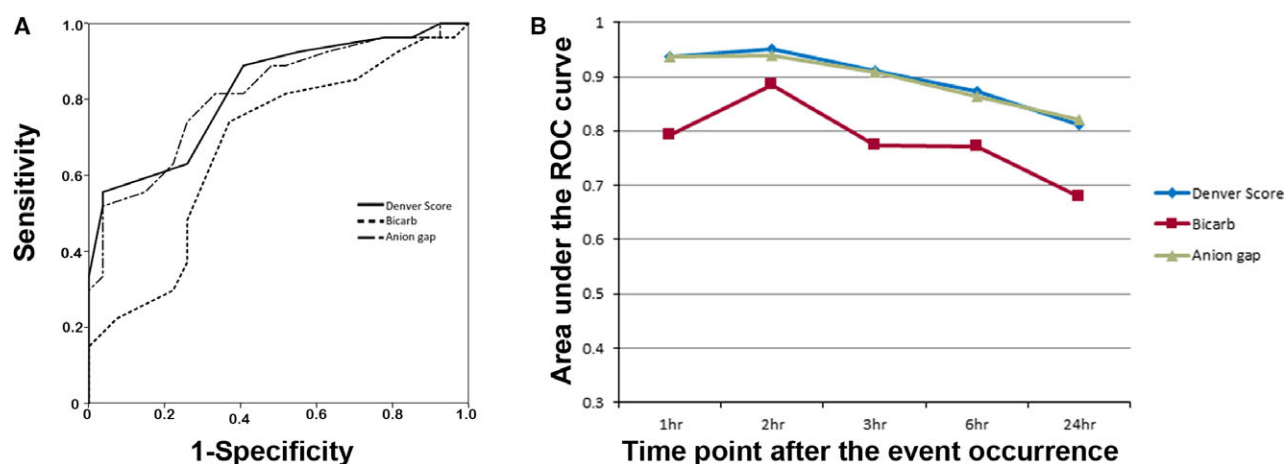


Figure 1.

Sensitivity and specificity of Denver Seizure Score, bicarbonate level, and anion gap for detection of generalized convulsive epileptic seizures (vs. psychogenic nonepileptic seizures). **(A)** Receiver operating characteristic (ROC) curves. **(B)** Area under the curves for ROC curves plotted at different time points between laboratory draw and event occurrence.

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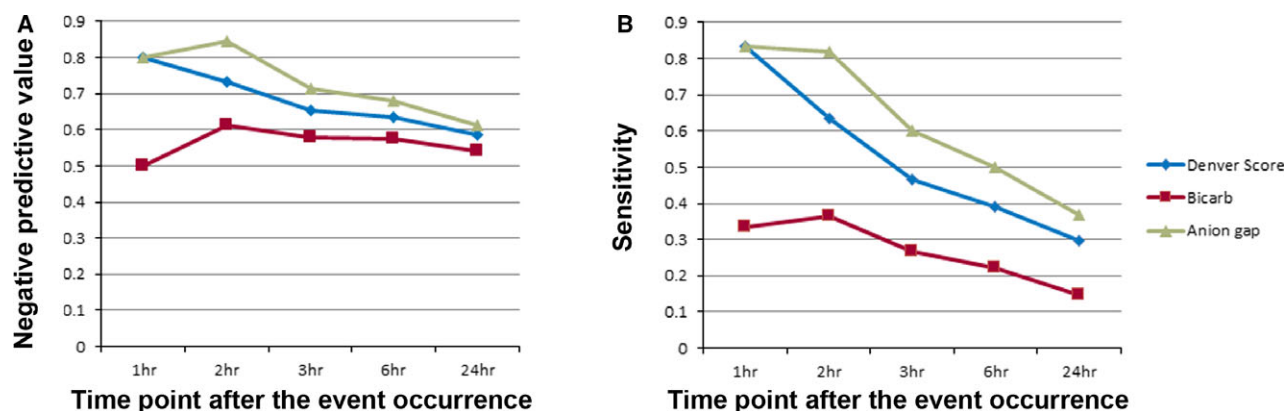


Figure 2.

Negative predictive values **(A)** and sensitivities **(B)** of Denver Seizure Score ≥ 0 , anion gap > 10 , and bicarbonate < 20 for detection of generalized convulsive epileptic seizures (vs. psychogenic nonepileptic seizures) when samples are drawn at different time points after the event. Positive predictive value and specificity were 100% at all time points for each series.

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definitively explain why AG is a better measure than bicarbonate.

Acidosis has been shown after ES when subjects' blood samples were obtained 15 min to 1 h after the seizure was witnessed by neurologists.¹ We show that this association exists up to 24 h after the generalized convulsive epileptic seizure event. Metabolic acidosis has also been demonstrated during vigorous exercise.³ However, it has not previously been explored whether a similar phenomenon is present in PNES with generalized body movements. Our study, for the first time, showed that the bicarbonate level and AG following PNES remained stable in the first 24 h after the event in our sample population. It may be possible that PNES generalized movements are not vigorous enough to induce anaerobic metabolism.

Various biomarkers have been explored to help differentiate PNES and ES. Prolactin has been used in the ED, as it has high specificity for ES if the sample is drawn within hours of the event,⁴ but it has also been shown to be false positive in up to 14% of PNES patients.^{5–7} In addition, changes of prolactin after repetitive epileptic seizures have shown inconsistent results and have been reported either lower than normal baseline⁶ or remarkably increased,⁵ making prediction with prolactin level limited, especially when patients have clustered episodes. Other biomarkers, such as serum adrenocorticotrophic hormone and cortisol level, have also been shown to have dynamic changes prior to and after generalized tonic–clonic seizures, but not during PNES episodes.⁸ However, they are rarely used in clinical settings, because they are only

applicable when the patients already has a baseline level for comparison. In addition, heart rate variability (HRV) change during seizure has drawn great interest; however, there were no statistical differences in HRV parameters between PNES and epilepsy patients.⁹ Recently, a pilot study also investigated the possibility of using postictal ammonia to help differentiate between PNES and ES, with the sample drawn within a limited window of 15–60 min after the event.¹⁰ In our study, we showed that AG > 10 also has high specificity for ES, with the advantage of maintaining this specificity up to 24 h after the event. Furthermore, AG is an easily obtainable laboratory test with rapid turnaround time, which is not always the case with prolactin or other hormone biomarkers mentioned above.

Our study has several important limitations. Although all our subjects in the ES group had described semiology consistent with a generalized convulsive epileptic seizure and an abnormal interictal EEG, ictal video-EEG was not obtained in these subjects. Retrospective design precluded us from identifying patients with video-EEG-confirmed ES. Despite limitations, we are able to demonstrate a significant difference, which could be used as potential evidence to support further investigation of involving prospective AG determination at serial time points following inpatient video-EEG diagnosis of an event, to further validate AG as a specific biomarker for ES when applied to a random mixed sample of ES and PNES subjects.

DISCLOSURE

The authors declare no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Study sample characteristics.