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Potential use of leukocytosis and anion gap elevation in differentiating psychogenic nonepileptic seizures from epileptic seizures

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Summary

Epileptic seizures (ES) and psychogenic nonepileptic seizures (PNES) can be difficult to differentiate from each other in the emergency department (ED) setting. We have previously shown that the anion gap (AG) can help differentiate between ES and PNES in the ED. In this study, we explored whether additionally considering leukocytosis can help better differentiate between ES and PNES. We screened a total of 1354 subjects seen in the ED of a tertiary care medical center; 27 PNES and 27 ES patients were identified based on clinical description and subsequent electroencephalography (EEG). Multivariable logistic regression analysis was used to model the association between ES, leukocytosis, and AG. Our results indicated that within 9 hours after the index event, serum AG (adjusted odds ratio [aOR] 2.07) and white blood cell (WBC) count (aOR 1.61) were both independently associated with ES. We derived an equation to help differentiate between ES and PNES: 1.5*AG+WBC. A score >24.8 indicated a >90% likelihood of ES. A score <15.5 indicated a <10% likelihood of ES (ie, the alternate diagnosis of PNES should be considered). This study for the first time provides evidence to help differentiate PNES and ES utilizing acidosis and leukocytosis.

KEYWORDS

acidosis, anion gap, leukocytosis, nonepileptic seizure, seizure

1 | INTRODUCTION

Differentiating between epileptic seizures (ES) and psychogenic nonepileptic seizures (PNES) is a commonly encountered problem for neurologists. The symptoms of these 2 diseases can be difficult to differentiate, especially in the emergency department (ED) setting, where patients often present following their events without clear witnessed history. This limitation can lead to a tendency to treat the patients as though they had ES. Studies have shown that patients often get misdiagnosed, with a mean PNES diagnosis delay of 7.2 years.[1] The estimated lifetime cost of PNES misdiagnosis was appreciated as $100 000 per patient, and the annual cost of PNES misdiagnosed as ES can be estimated between $650 million and $4 billion in the United States.[2]

In this study, we explored whether the combination of transient leukocytosis and acidosis could help to differentiate these 2 clinically similar but pathophysiologically different diseases in the ED setting, by analyzing the complete blood (cell) count (CBC) and anion gap (AG).

2 | METHODS

2.1 | Study design and selection criteria

This study was conducted with a retrospective chart review on patients who visited a tertiary care medical center emergency room (University of Massachusetts Memorial Hospital, Worcester, MA) between January 1, 2014 and June 30, 2016. The study was performed with approval and in accordance with the guidelines of the institutional review board (H00010215) at the University of Massachusetts Medical School.

The patient cohort with inclusion and exclusion criteria has been described previously.[3] The inclusion criteria were the following: (a) ED diagnosis of "generalized seizures," "generalized shaking episodes," or "seizures" for adult patients older than 18; and (b) a well-documented spell onset within 24 hours of a basic metabolic panel (BMP) and CBC obtained in the ED. The exclusion criteria were the following: (a) patients had other documented active medical problems that could cause acidosis or leukocytosis, and confound the analysis, such as sepsis, alcohol, or medicine toxicity; and (b) patients who were taking medications that could cause metabolic acidosis (such as topiramate, zonisamide, hydrochlorothiazide, acetaminophen, diuretics, and steroids) were excluded unless they had a baseline normal BMP within the 12 weeks preceding their presentation on the same medications.

Patients were subsequently assigned to ES and PNES groups. All the patients included in the ES group had (a) documented semiology of the event that was consistent with a generalized convulsive seizure; (b) an abnormal interictal electroencephalography (EEG) showing epileptiform discharges; and (c) did not have repetitive seizures that occurred within 6 hours to avoid the potential influence of the repetitive episodes on the study analysis. All the patients included in the PNES group had spells with "generalized body jerking" and had subsequent video-EEG capturing similar events confirming the diagnosis of PNES. The PNES patients with semiology of non-motor symptoms were excluded.

2.2 | Statistical analysis

The continuous variables are reported as mean ± standard deviation (SD). Between-group comparisons for continuous variables were made with Student t test. Multivariable logistic regression analysis, receiver-operator characteristic (ROC) curves, and Hosmer-Lemeshow goodness-of-fit test were used to investigate the association between the probability of AG, white blood cell (WBC) counts, and probability of having ES. Once an adjusted logistic regression model was fit, the estimated coefficients were used to create a linear equation to predict the probability, >90% and <10%, of

> **Key Points**
>
> - Differentiating between ES and PNES is a commonly encountered issue for neurologists
> - The mean AG was elevated in the ES group within the first hour until the 24-hour period after the event, when compared to the PNES group ($P < 0.05$)
> - Elevation of WBC count was also observed in the ES group when compared to the PNES group, with significant differences seen starting 2 hours after the event ($P < 0.05$)
> - The area under the curve (AUC), sensitivity, and negative predictive value of AG and WBC count to differentiate ES from PNES decreased as time progressed
> - An equation was derived for patients who had an index event within 9 hours: 1.5*AG+WBC; a score >24.8 indicates a >90% likelihood of ES

having ES. An alpha level of 0.05 was considered to assess statistical significance. SAS 9.4 (SAS Institute Inc., Cary, NC) was used for statistical analysis.

3 | RESULTS

3.1 | Demographic and clinical characteristics

Among the total screened 1354 patients, 126 met inclusion criteria. Of these, 72 were excluded because they had other medical conditions, toxicities, or chronic medications that could cause metabolic acidosis. Of the remaining 54 patients, enough medical record information was available to stratify 27 to the ES group and 27 to the PNES group. There were no significant differences in gender or mean age between the group of PNES and ES patients (Table S1). Antiepileptic medications used by the patients in the final cohort included levetiracetam, zonisamide, valproic acid, gabapentin, phenytoin, oxcarbazepine, lorazepam, and diazepam.

3.2 | Dynamic changes of leukocytosis and acid-base equilibrium in the ES vs PNES patients

As shown in Table 1, subjects were grouped 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 mean AG was elevated in the ES

TABLE 1 Study sample characteristics

	0-1 h PNES	ES	P-value	0-2 h PNES	ES	P-value	0-3 h PNES	ES	P-value
WBC count (4.0-10.4 × 10³/µL)	5.80 ± 2.28	11.97 ± 5.04	0.053	6.99 ± 1.85	10.62 ± 4.96	0.034	7.16 ± 1.87	10.73 ± 4.5	0.010
Bicarb (24-32 mEq/L)	24.75 ± 3.78	21.00 ± 2.83	0.108	25.64 ± 2.5	20.18 ± 4.81	0.003	24.8 ± 2.88	21.2 ± 4.54	0.015
AG (5-15 mEq/L)	5.50 ± 4.12	15.5 ± 5.01	0.011	5.64 ± 2.58	14.18 ± 5.00	<0.001	5.53 ± 2.2	12.4 ± 5.28	<0.001
Na (135-145 mEq/L)	137.50 ± 2.65	136.83 ± 7.25	0.867	137.36 ± 1.75	137.82 ± 5.46	0.795	137.2 ± 1.57	137.27 ± 5.43	0.964
K (3.5-5.3 mEq/L)	4.53 ± 1.07	4.08 ± 0.66	0.439	4.05 ± 0.78	4.00 ± 0.56	0.852	3.97 ± 0.68	4.08 ± 0.51	0.610
Cl (97-110 mEq/L)	107.25 ± 2.76	100.33 ± 7.84	0.134	106.09 ± 2.84	103.45 ± 7.10	0.267	106.53 ± 2.75	103.67 ± 6.7	0.137
Age (y)	43.00 ± 16.08	48.50 ± 22.65	0.688	35.36 ± 12.77	43.18 ± 19.34	0.277	33.67 ± 12.55	48.2 ± 22.63	0.038

	0-6 h PNES	ES	P-value	0-9 h PNES	ES	P-value	0-24 h PNES	ES	P-value
WBC count (4.0-10.4 × 10³/µL)	6.92 ± 1.78	11.04 ± 4.14	<0.001	7.06 ± 1.75	10.66 ± 4.35	<0.001	7.78 ± 2.97	10.22 ± 4.14	0.022
Bicarb (24-32 mEq/L)	25 ± 2.79	21.56 ± 4.26	0.006	25 ± 2.93	21.77 ± 3.93	0.004	24.93 ± 2.89	22.63 ± 4.19	0.024
AG (5-15 mEq/L)	5.79 ± 2.04	11.56 ± 5.24	<0.001	5.76 ± 2.1	11.09 ± 4.85	<0.001	5.85 ± 2.03	10.37 ± 4.76	<0.001
Na (135-145 mEq/L)	137.42 ± 1.46	136.78 ± 5.31	0.614	137.19 ± 1.69	136.73 ± 4.86	0.682	137.56 ± 2.26	137.07 ± 4.46	0.714
K (3.5-5.3 mEq/L)	4.01 ± 0.62	4.07 ± 0.5	0.743	4.02 ± 0.59	4.02 ± 0.47	0.982	3.96 ± 0.56	4.02 ± 0.45	0.294
Cl (97-110 mEq/L)	106.37 ± 2.61	103.67 ± 6.33	0.095	106.19 ± 2.54	103.86 ± 5.75	0.096	106.59 ± 2.55	104.07 ± 5.31	0.050
Age (y)	36.74 ± 14.65	49.33 ± 22.96	0.053	37.24 ± 14.07	44.32 ± 23.38	0.239	36.78 ± 13.67	42.15 ± 21.71	0.591

group compared to the PNES group from as early as within the first hour until the 24-hour period after the event ($P < 0.05$). Elevation of WBC count was also observed in the ES group when compared to the PNES group, with significant differences seen starting at a later time (2 hours after the event) and persisting until 24 hours ($P < 0.05$, separately).

3.3 | Efficacy of transient leukocytosis and AG changes to help differentiate PNES from ES

The ROC curve for sensitivity and specificity of ES detection was plotted for AG and WBC count. Areas under the ROC curve (AUC) within 24 hours were 0.822 and 0.688, respectively (Figure S1). The AUC, sensitivity, and negative predictive value decreased as time progressed (Figure S2).

3.4 | A model of utilizing WBC count and AG to help differentiate between ES and PNES

Multivariable logistic regression analysis was used to model the association of probability of having ES using both variables of WBC count and AG at different durations up to 24 hours. At the time interval beyond 12 hours between the spell and the blood draw, the sensitivity of WBC count dropped out and did not contribute to the model in a statistically significant manner. When modeled using logistic regression with a cutoff of 9 hours, serum AG (adjusted odds ratio [aOR] 2.07) and WBC count (aOR 1.61) were both independently associated with ES. By defining the probability of high (>90%), intermediate (10%-90%), and low (<10%), we derived a score to help predict a patient's likelihood of having ES vs PNES based on the AG and WBC counts. When 1.5*AG+WBC is >24.8, the patient has a high likelihood of ES; whereas when 1.5*AG+WBC is <15.5, the patient has a low likelihood of ES, hence the alternate diagnosis of PNES should be considered (Figure 1).

4 | DISCUSSION

Our study suggests that the dynamic changes of leukocytosis and acid-base disequilibrium could be used to help differentiate between ES and PNES. The first of these changes was anion gap (or AG) elevation. Transient leukocytosis is not a sensitive but specific marker to different between ES and PNES. By using these 2 markers, we proposed a score to help evaluate whether the patients with a generalized shaking event had a high or low likelihood of ES.

In this present study, we demonstrated that the transient leukocytosis associated with ES persisted up to 9 hours after the event, but not in the PNES group. The possible pathophysiologic mechanism of seizure-related leukocytosis could be demargination of deposited leukocytes caused by high levels of catecholamines.[4] Previous studies have shown that the incidence of leukocytosis after generalized seizures was variable at around 30%-62.5% using different time cutoffs,[4–6] which was consistent with our finding that
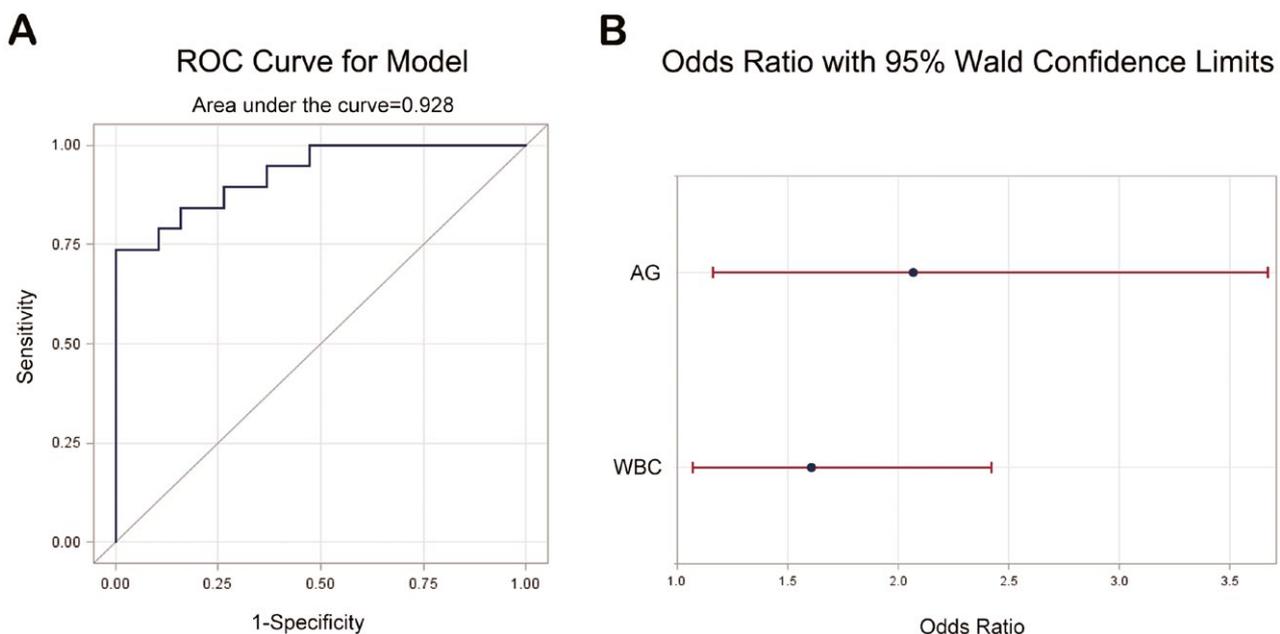

FIGURE 1 The association of ES, WBC count, and anion gap in the first 9 hours after the event with multivariable regression modeling. The ROC of the modeling was 0.925. A, Serum AG (adjusted odds ratio 2.07, 95% CI 1.17-3.67) and WBC count (adjusted odds ratio 1.61, 95% CI 1.07-2.42) were both independently associated with ES. B, Hosmer-Lemeshow goodness-of-fit test P-value for this modeling was 0.77, leading us to conclude that there is no evidence that the model does not fit the data. The C-statistic was 0.93, indicating the model has good discrimination

leukocytosis is not a highly sensitive, but rather a specific biomarker for ES vs PNES (Figure S2). Transient leukocytosis is a well-known phenomenon after exercise and is determined mainly by the intensity and duration of the physical exertion. Although the PNES patients in this cohort were reported to have generalized body shaking, we suspect that their activity was less intense than that of the generalized tonic-clonic seizures in the ES group, and that the intensity of this physical stress was inadequate to induce leukocytosis.

In addition, the time that elapsed since the shaking spell is also vital for the dynamic changes of both leukocytosis and AG level. Acidosis occurs within 1 hour after ES and appears in a very transient pattern as we reported previously.[3] The phenomenon of leukocytosis, defined as increased WBC count (the normal range of WBC is $4.0\text{-}10.4 \times 10^3/\mu L$ in our study cohort), can be seen in various situations such as inflammation, inflammatory diseases, and stress. When we compared the mean value of WBC count in the 2 different groups, it showed significant difference between ES and PNES with a slight lag from 2 hours to 9 hours after the event, and soon resolved beyond this period in our study. Similar dynamic leukocytosis response has been reported after strenuous exercise with a peak time of 2-4 hours afterward.[7] There have been proposals that it could be due to catecholamines produced during exercise, which act to increase the ratio of circulating to noncirculating leukocytes, and cortisol, which involves a time lag to increase the total number of leukocytes in the vascular compartment. Although our data did not show a significant difference of WBC counts between these 2 groups within the first hour, the limits of our sample size may not capture the significant difference that was noted in later time points with a larger sample size.

Other studies have tried to investigate potential biomarkers to help identify ES from other alternative diagnosis, such as prolactin level, serum lactate level, hormone changes, as well as postictal ammonia. Each of these also has their own merits and disadvantages. Prolactin level was also elevated after PNES,[8] and the pattern of changes varies if patients have repetitive seizures.[9] Ammonia and lactate required narrow time windows (<1 hour, and 2 hours, respectively) to observe the changes.[10,11] The biomarkers proposed in our study allow longer duration between the event and the time of blood being drawn, and they are routinely drawn in this setting, which usually has a rapid turn-around, and hence are more practical in daily practice. Recent studies have shown that surface electromyography might help distinguish between convulsive PNES and ES.[12] In addition, a scoring system of clinical history and comorbidities has been proposed to diagnosis PNES, which achieved promising results.[13,14] Further studies of investigating the combination of the preceding methods and the concomitant AG and WBC cell biomarker changes for increasing the accuracy of determination of PNES vs ES would be interesting to pursue.

Our study also has limitations. All the subjects recruited in the ES group had described semiology consistent with a generalized convulsive seizure and an EEG observation of at least interictal epileptiform discharges, but no ictal video-EEG was obtained in these subjects due to the retrospective limitations of the study. Similarly, the shaking spell in patients in the PNES group patients before ED admission was not recorded in real-time with video-EEG, but similar events with same description of semiology were identified with subsequent video-EEG to confirm their diagnoses. Although the patients in the PNES group had similar semiology, with their index events identified and diagnosed by video-EEG, it is possible that some patients may have had a mixed ES and PNES disorder. In addition, the overall sample size is moderate. Although our study does show a significant difference between the 2 groups (generalized tonic clonic seizures vs PNES) and the regression model does fit the data well, future prospective studies with larger sample size are warranted for further validation.

In summary, the tool of 1.5*AG+WBC proposed in the current study could be helpful as another piece of evidence for diagnostic consideration when confronted with this common situation in the emergency setting.

DISCLOSURE

None of the authors has any conflicts of interest to disclose. 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.

AUTHOR CONTRIBUTIONS

Yi Li: Study design, data analysis, writing up the manuscript; Liesl Matzka: data analysis and critical review; Julie Flahive: statistical analysis and critical review; Daniel Weber: study concept and design and critical revision of manuscript for intellectual content.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.