Value of anion gap in differentiating between epileptic and psychogenic seizures

Abdelnasser A. Morad, Maged K. Fahem, Shimaa M. Kasem, Raghda A. Abdel-Halem, Amgad A. Saad

Neuropsychiatry Dept., Faculty of Medicine, Benha Univ., Benha, Egypt

E-Mail: amgad.anis@fmed.bu.edu.eg

Abstract

Background: Epilepsy is defined as permanent tendency of the brain to generate epileptic seizures. Differentiation between psychogenic non-epileptic seizures (PNES) and generalized convulsive epileptic seizures (ES) is important for therapeutic decision making in the emergency department (ED). Up to one fifth of patients who present with seizures do not have epilepsy. The majority suffer from psychologically mediated episodes; dissociative seizures, often referred to as ‘‘non-epileptic seizures’’. Most patients are falsely treated for epilepsy for several years with more antiepileptic drugs (AEDs) at higher doses and with more side effects. Anion gap (AG) is the difference in concentration between unmeasured anions and unmeasured cations. We can estimate the value of anion gap according to the following equation: Anion gap= Na^+- (HCO_3^- + Cl^-). Clinician uses anion gap to classify acid–base disorders. Tonic-clonic seizures (TCS) either generalized onset (GTCS) and focal to bilateral tonic-clonic seizures (FBTCS), are commonly associated with strong and sustained convulsions of a large number of body muscles along with respiratory arrest and tachycardia, leading to considerable metabolic stress which can be assessed by anion gap.

Methods: The study was conducted through comparing results of anion gap analysis between 2 groups of patients who present with generalized shaking attacks according to non-medical witnesses. The study included 60 patients, recruited from ER in Benha university hospitals in 2021, divided in 2 groups, each is 30 patients. One group had true ES and the other group had PNES according to a neurologist observer.

Results: There was a significant difference between anion gap values of different groups. ES: 17.79 ± 5.49 range (6.6 - 35) and PNES: 13.45 ± 2.85 range (7.6 – 18.7), $p<0.001$. Bicarbonate (HCO_3^-) values were also of statistically significant difference as found in ES: 18.36 ± 4.32 range (10.2 – 25.9) and in PNES: 21.54 ± 2.73 range (15 – 28.7), $p=0.001$.

Conclusion: Seizures are encountered a lot in ER and considered as a neurological emergency that needs to be clearly distinguished from other mimics mostly PNES to choose the right management. Anion gap value can be used to assure the type of seizures within 2 hours especially if seizures arenot witnessed by a neurologist to determine its type. Anion gap ≥ 16 has accuracy of 75% in detecting type of shaking attacks.

Keywords: ES, PNES, seizures, epileptic, anion

Introduction

Epilepsy is permanent tendency of the brain to generate epileptic seizures. These result of an abnormal synchronous activity of nerve cell associations. Diagnosis of epilepsy can be made through 2 unprovoked seizures at a time interval of 24 hours after the first epileptic seizure (Baumgartner and Surges 2019).

Differentiation between PNES and ES is important for therapeutic decision making and appropriate triaging of patients in the ED. This can be difficult, as the event concerning for seizure is often not witnessed by a medical professional and semiology descriptions from lay witnesses can be misleading (Li et al. 2019).

Up to one fifth of patients who present to specialist clinics with seizures do not have epilepsy. The majority of such patients suffer from psychologically mediated episodes; dissociative seizures, often referred to as ‘‘non-epileptic seizures’’. Diagnostic errors are the rule rather than an exception. Most patients are treated for epilepsy for several years and by the time the correct diagnosis is made they will commonly have taken more antiepileptic drugs at higher doses and experience more side effects than an equivalent cohort of patients with epilepsy (Mellers 2005).

Unclear transient alterations of consciousness present an interdisciplinary diagnostic challenge in the emergency room. One of the main questions in the process of differential diagnosis remains the distinction between epileptic and non-epileptic episodes, particularly syncopes and psychogenic non-epileptic seizures (PNES) (Olaciregui Dague et al. 2018).

Anion gap (AG) is the difference in concentration between unmeasured anions and unmeasured cations according to following equation: Anion gap= Na^+- (HCO_3^- + Cl^-). Clinician uses anion gap usually to classify acid–base disorders (Lolekha et al. 2001).

Tonic-clonic seizures (TCS), that is, generalized onset tonic-clonic seizures (GTCS) and focal to bilateral tonic-clonic seizures (FBTCS), are commonly associated with strong and sustained convulsions of a large number of body muscles along with respiratory arrest and tachycardia, leading to considerable metabolic stress (Nass et al. 2019).

This study is investigating anion gap usefulness in differentiating epileptic seizures from psychogenic non-epileptic seizures in emergency room.

Patients and methods:

This study was conducted in the ER of Benha university hospitals, during the period of December 2020 to July 2021.

Type of study

Comparative cross sectional study.

Sample size:

A total of 60 patients divided in 2 groups, each is 30 patients.

- **ES group**: 30 patients presenting with true epileptic seizures (witnessed by a neurologist).
- **PNES group**: 30 patients presenting with psychogenic seizures (witnessed by a neurologist).

Sampling:

Participants will be chosen by non-random technique, all patients with generalized shaking attack or generalized stiffening attack fulfilling the inclusion criteria and agree to participate will be included in the study.

Inclusion criteria:

All patients included in this study are older than 18 years old who present to emergency setting within 2 hours of supposed seizures.

Exclusion criteria:

All patients presenting with comorbidity which can cause acidosis and change in anion gap calculations e.g. sepsis, DKA, drug toxicity …etc.

Ethical consideration:

The study protocol was approved by Ethical Committee of Faculty of Medicine Department of neuropsychiatry at Benha University. Written consent was taken for every participant.

All patients were subjected to the following:

1. Complete medical history.

2. Physical examinations & neurological examination.
3. Electrocardiogram ECG.
4. Laboratory:
    - Arterial blood gas.
    - Liver function test.
    - Kidney function test.
    - Lipid profile.
    - Complete blood count.
5. Radiological: CT brain and / or MRI brain with DWI.
6. Electroencephalography EEG.

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was

used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at p-value < 0.05.

Results:

In ES, The mean age was 38.8 years with standard deviation of 16.5 years ranging from 18-65 years. While in PNES, The mean age was 28.1 years with standard deviation of 8 years ranging from 18 - 47 years and it was significant p<0.05. Table (1)

In ES, males were (60%) while in PNES males represented (33.3%) p=0.038 significant. Table (1)

In ES group, married patients (53%), while single patients were (33%) and divorced patients were (13%). In PNES married patients were (50%), while single patients were (43.3%) and divorced patients were (6.7%) p=0.3 non-significant. Table (1)

No significant difference regarding residence or occupation between both groups. Table (1)

Causes of seizures in ES group are mentioned in table (2)

Criteria observed during PNES are collected in table (3) with most movements are:

- Stiffness of upper limb 30%
- Peripheral tremors 26.7%
- Bizarre movements 23.3%
- Forced eye closure 20%
- Stiffness of lower limb 20%
- Forced mouth closure 16.7%

Imaging in epileptic group (abnormal in 46.7%) and PNES group (abnormal in 6.7%) was significantly higher, p <0.001. Table (4)

Lesions detected in imaging of ES group cases. Table (5) mostly are

- Cerebrovascular strokes 42.8%
- Tumers 28.5%
- Atrophied brain tissue 14.2%

EEG in epileptic group (abnormal in 50%) and PNES group (abnormal in 6.7%) was significantly higher, p <0.001. Table (6)

Comparing values of serum bicarbonate anions in epileptic group (M=18.36, SD=4.32) and these of PNES group (M=21.54, SD=2.73) was significantly higher, p = 0.001. Table (7)

Comparing scores of anion gap in epileptic group (M=17.797, SD=5.492) and these of PNES group (M=13.45, SD=2.859) was significantly higher, p<0.01. Table (8)

Accuracy measures of Anion gap in detecting true epileptic fits when AG≥16:
Sensitivity 70%, specificity 80%, negative predictive value 73%, positive predictive value 78% and accuracy 75%. Table (9)

Area under the curve AUC was 0.75. Fig (1)

Multivariate logistic regression revealed that anion gap cut off value ≥ 16 was a predictor for seizures event to be true epileptic (OR = 9.333 & 95% CI ranged from 2.847 – 30.602). P value was < 0.01. Table (10)

In ES group: There was a significant, moderate, negative monotonic correlation between anion gap values and time elapsed before blood sample is taken (rS=-0.46, n=30, p<.05). Fig (2)

In PNES group: Correlation between anion gap values and time elapsed was non-significant P=0.3. Fig (3)

Table (1):socio-demographic data of both groups

		ES n=30	PNES n=30	Test of significance	P value
Age in years	Mean±SD	38.8±16.5	28.1±8	ZMWU=2.45	0.014 S
	Min - Max	18-65	18-47		
Sex	Males	18 (60%)	10 (33.3%)	X2=4.286	0.038 S
	Females	12 (40%)	20 (67.7%)		
Marital State	Single	10 (33.3%)	15 (50%)	X2=1.977	0.372 NS
	Married	16 (53.3%)	13 (43.3%)		
	Divorced	4 (13.3%)	2 (6.7%)		
Residence	Urban	18 (60%)	14 (46.7%)	X2=1.071	0.3 NS
	Rural	12 (40%)	16 (53.3%)		
Occupation	Student	3 (10%)	7 (23.3%)	X2=2.729	0.435 NS
	Employee	6 (20%)	4 (13.3%)		
	Manual worker	8 (16.7%)	5 (16.7%)		
	Unemployed	13 (43.3%)	14 (46.7%)		

Table (2): Causes of seizures in ES group

Possible cause	No(30)	Percentage (100%)
No obvious cause	8	26.7%
CVS	7	23.3%
Infection	3	10%
Tumor or excised mass	5	16.7%
Birth injury	3	10%
Post traumatic	4	13.3%

Table (3):Criteria/Movements observed during PNES

	Frequency	%
Sounds Before/during seizure attack	5	16.7%
Bizzare movements	7	23.3%

Stiff lower limbs	6	20%
Stiff upper limbs	9	30%
Teeth clenching	5	16.7%
Facial contractions	3	10%
Side to side turning	2	6.7%
Forced eye closure	6	20%
Peripheral tremors	8	26.7%

Table (4): Imaging (CT brain or MRI if available) in the 2 groups

		ES n=30	PNES n=30	Chi square	P value
Imaging (CT or MRI)	No changes	16 (53.3%)	28 (93.3%)	X2= 12.273	<0.001 HS
	Abnormal finding	14 (46.7%)	2 (6.7%)		

Table (5): lesions detected in imaging of ES group cases

Lesion	N=14	100%
Stroke*	6	42.8%
Tumor with/without surgical intervention	4	28.5%
Brain atrophy	2	14.2%
Congenital anomalies	1	7.1%
Brain edema	1	7.1%

*Stroke: includes brain infarction(arterial or venous), hemorrhage, reversible encephalopathy syndrome

Table (6): Electro-encephalograph in both groups

		ES n=30	PNES n=30	Chi square	P value
EEG	No changes	15(50%)	28 (93.3%)	X2= 13.871	<0.001 HS
	Abnormal finding	15 (50%)	2 (6.7%)		

Table (7): Difference of bicarbonate values between ES & PNES groups

		ES n=30	PNES n=30	T test	P value
$HCO3^-$ In ABG analysis	Mean±SD	18.36±4.32	21.54±2.73	3.411	0.001 HS
	Min-Max	10.2 – 25.9	15 – 28.7		

Table (8): Difference of AG values between ES & PNES groups

		ES n=30	PNES n=30	T test	P value
Anion Gap	Mean±SD	17.797±5.492	13.45±2.859	3.845	<0.001 HS
	Min - Max	6.6 - 35	7.6 – 18.7		

Table (9): Accuracy measures of Anion gap in detecting true epileptic fits When AG ≥ 16	
sensitivity	70%
specificity	80%
NPV	73%
PPV	78%
Accuracy	75%
AUC	.75

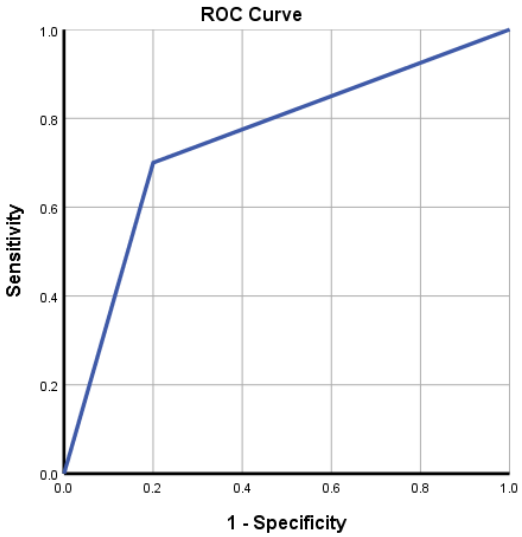

Figure 1 ROC curve

Table(10): Anion gap for prediction of true seizure events:

	B	Wald	OR	95% C.I. for OR	P value
Anion gap≥16	2.234	13.591	9.333	2.847 – 30.602	0.0001

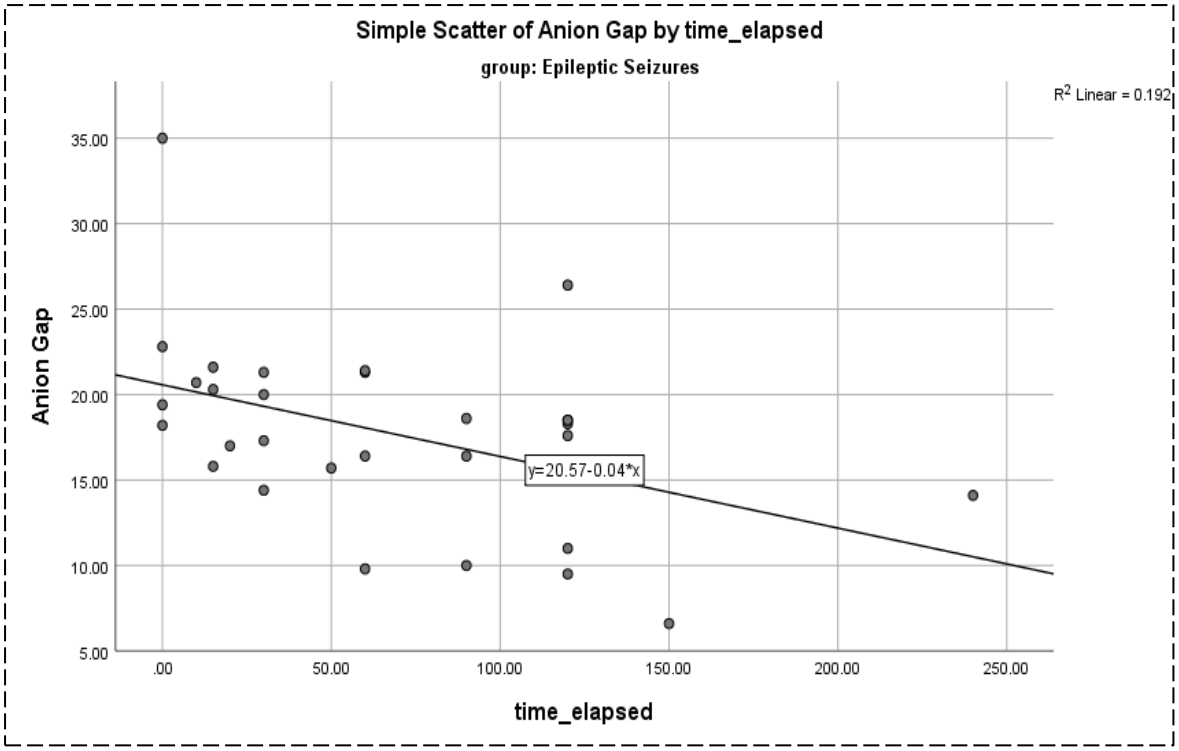

Figure 2 AG versus time in ES

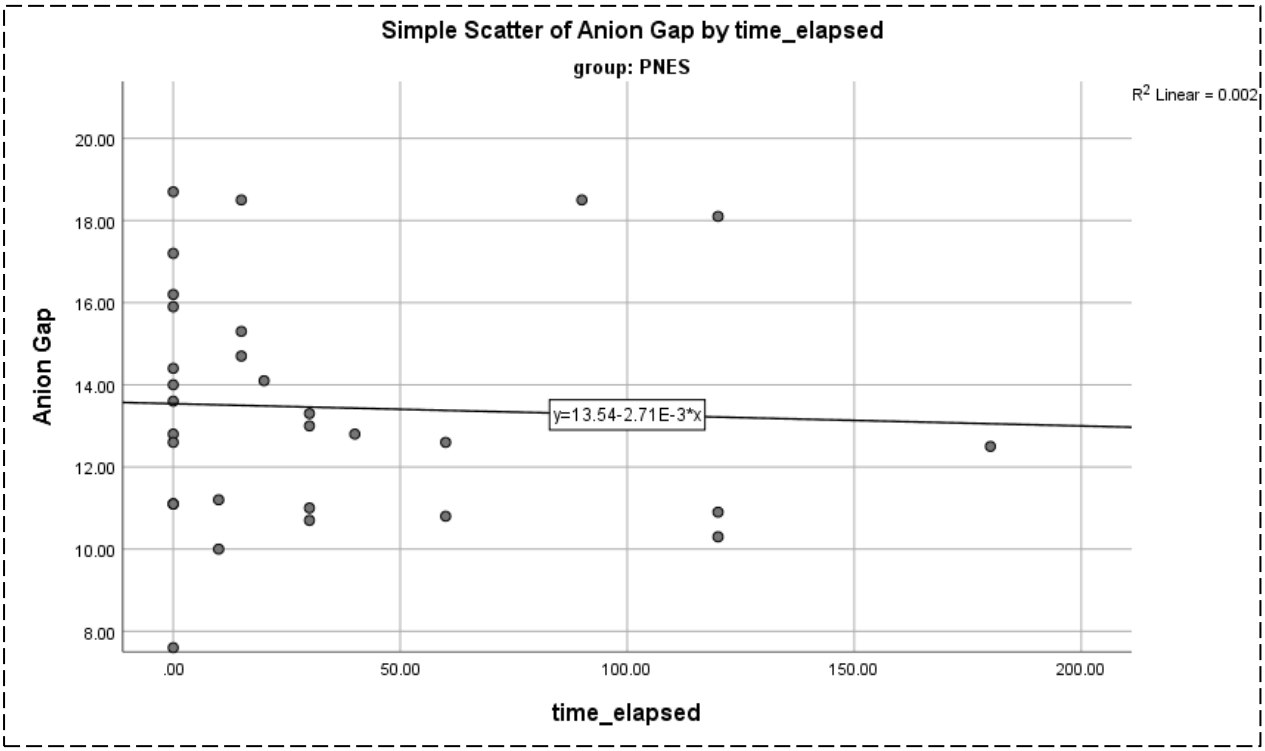

Figure 3AG versus time on PNES

Discussion:

This study is a descriptive cross-sectional study conducted at Benha University hospital, aimed to assess the value of anion gap to differentiate between epileptic seizures and psychogenic seizures in patients presenting to emergency room with shaking attacks. The studied sample was 60 patients divided in 2 groups, each group had 30 patients fulfilling inclusion criteria.

In epileptic seizures group, the mean age was 38.8 years with standard deviation of 16.5 years ranging from 18 - 65 years; while in psychogenic non-epileptic seizures group the mean age was 28.1 years with standard deviation of 8 years ranging from 18 - 47 years, p=0.014. This was significant difference between both groups. Age results in PNES are consistent with the mean and median age at onset of psychogenic non-epileptic seizures which is around 28 years by (Ganju and India 2019; Goldstein et al. 2019; Asadi-Pooya and Sperling 2015). The age mean is 80 years by (Falco-Walter 2020; Neligan, Hauser, and Sander 2012) which is much higher than the sample studied here mostly due to small sample size and selection bias.

In epileptic seizures group, males are dominant (60%), p=0.038. this is not consistent with what (Falco-Walter 2020) detected, as their results show no difference in prevalence of epilepsy between both sexes. This is mostly because of small sample size in our study. While in psychogenic non-epileptic seizures, females are dominant (67.7%) and this was significant difference between ES and PNES groups. This female domination in psychogenic non-epileptic seizures group can be explained as psychogenic non-epileptic seizures is a dissociative disorder (Erro et al. 2016) which has a higher prevalence in females.

This study found that brain imaging of patients of epileptic seizures group had significant changes in 46.7% while that of psychogenic non-epileptic seizures group patients had 6.7% which was significant.

It may be explained by the fact that about 30% of the studied epileptic seizures group patients were recent onset seizures and most of them due to vascular causes. While in psychogenic non-epileptic seizures patients, 50% had negative comorbidity with seizures or other neurological problems.

Imaging studies in patients with psychogenic non-epileptic seizures have failed to detect on specific structural abnormalities across psychogenic non-epileptic seizures patients. (Ganju and India 2019; Mcsweeney, Reuber, and Levita 2017; Asadi-Pooya and Sperling 2015)

This study found that EEG of patients of epileptic seizures group had significant changes in 50% while that of psychogenic non-epileptic seizures group patients had 6.7% which was significant difference, p<0.001. About 33.3% showed generalized epileptogenic activity and about 67.7% showed focal epileptogenic activity.

This is consistent with statement of (Rosenow, Klein, and Hamer 2015) that EEG detects abnormality in 60% to 90% of epileptic patients. While in psychogenic non-epileptic seizures, there is no EEG changes. EEG is abnormal in 0.5% to 2.5% in non-epileptic healthy people. (Rosenow, Klein, and Hamer 2015)

Causes detected in the studied epileptic seizures patients were idiopathic (no obvious cause) in 26.7%, cerebrovascular stroke in 23.3%, tumors or masses in 16.7%, post traumatic in 13.3%, infections and history of birth injury were 10% each.

This is consistent with the finding of (Falco-Walter 2020) who mentioned that in adult epilepsy, about 41% is of unknown cause, 27% of structural causes e.g. masses, strokes, etc.., 26% due to genetic causes and 6% due to infections. (Bosak et al. 2019)

The incidence of seizures after stroke was found to be 8.9% in one published prospective study. This is an underestimation as seizures occurring at stroke onset were not taken in to account and non-convulsive spells are rarely recognized as such (De Reuck 2009)

This was consistent with what we found in this study, about 23.3% of epileptic seizures group was post stoke.

In a recent meta-analysis of over 118 studies with a pooled sample size of 17,478 patients, comorbid epilepsy was reported in 22% of cases on average. (Kutlubaev et al. 2018)

This average is less than what we got in this study, as about 50% of psychogenic non-epileptic seizures patients reported comorbidity with epilepsy. Also, our aim is to assess the possibility of mimicking true seizures even if in the family and not the same patient.

Most manifestations detected during observing psychogenic non-epileptic seizures patients in this study were consistent with observations by (Reuber et al. 2011) with most prevalent movements in our study were:

- Peripheral tremors in 26.7%
- Bizzare movements e.g. chewing, smaching, limb flexion, pelvic thrusting, arching of back in 23.3%
- Teeth clenching (forced mouth closure) in 16.7%

In this study, we found that bicarbonate (HCO3-) values varied significantly between epileptic seizures group (mean ± SD: 18.36 ± 4.32) range (10.2 - 25.9) while in psychogenic non-epileptic seizures (mean ± SD: 21.54 ± 2.73) range (15 - 28.7).

It is consistent with the results of (Li et al. 2019) who found levels of bicarbonate (HCO3-) values within 2 hours of the seizure attack are (20.18 ± 4.81) in epileptic seizures while in psychogenic non-epileptic seizures are (25.64 ± 2.5) p=0.003, which was significant difference

It was also consistent with another study by (Olaciregui Dague et al. 2018) who found significant difference between epileptic seizures [median: 22.6 mmol/l, range (7.1 – 33.2] and psychogenic non-epileptic seizures [median: 26.1 mmol/l, range (20.6 – 35.5)] p <0.001.

This is also consistent with the findings by (Li et al. 2017) who considered bicarbonate (HCO3-) values less than 20 a significant detector of epileptic seizures against psychogenic seizures.

It is also consistent with another study by (Bakes et al. 2011) who found significant difference between epileptic seizures [median: 17 mmol/l, range(14 - 34)] and psychogenic non-epileptic seizures [median: 23 mmol/l, range(20 - 24), p<0.0001].

In this study, we found that anion gap values varied significantly between epileptic seizures group (mean ± SD: 17.797 ± 5.492) range= (6.6 - 35) while in psychogenic non-epileptic seizures (mean ± SD: 13.45 ± 2.859) range= (7.6 - 18.7).

It is consistent with the results of (Li et al. 2019) who found anion gap values within 2 hours of the seizure attack are (14.18 ± 5.00) in epileptic seizures while in psychogenic non-epileptic seizures are (5.64 ± 2.58) p<0.001, which was significant difference

It was also consistent with another study by (Olaciregui Dague et al. 2018) who found significant difference between epileptic seizures [median: 14.5 mmol/l, range (1.1 – 36.3] and psychogenic non-epileptic seizures [median: 9.7 mmol/l, range (2.1 – 16.7)] p <0.001.

It is also consistent with another study by (Bakes et al. 2011) who found significant difference between epileptic seizures [median: 21 mmol/l, range(9 - 42)] and psychogenic non-epileptic seizures [median: 13 mmol/l, range(7 - 21), p<0.0001].

Anion gap cut value in our study was ≥16 with sensitivity = 70% and specificity = 80%.

This is different from anion gap values by (Li et al. 2017) which were >10 with sensitivity = 81.8% and specificity = 100% in diagnosis of epileptic seizures against psychogenic non-epileptic seizures.

The cut-off value for AG by (Olaciregui Dague et al. 2018) varied only slightly to the general collective, and was 12.1 for both men (sensitivity 76.7%, specificity 91.7%) and women (sensitivity 56.5%, specificity 79.4%)

Conclusion:

An epileptic seizure is a temporary occurrence of manifestations due to increased brain synchronous neuronal activity. These manifestations may include body shaking involving the whole body or just a part.

Seizures with bilateral motor involvement often have a stiffening (tonic) Phase, followed by a muscle jerking (clonic) phase, and are known as tonic-clonic seizures.

The differential diagnosis of an epileptic seizure must be in mind during assessment of a person with a first seizure for fear of a "seizure mimic". The most important mimic is dissociative disorders and psychogenic non-epileptic seizures

PNES are not well characterized, and are therefore, confusing. This puts patients with PNES at risk of receiving unnecessary medications (e.g., antiepileptic drugs), emergency treatments, and even hospital admissions.

The most definitive way to diagnose epilepsy and the type of seizure is clinical observation of the seizure, although this often is not possible, except when seizures are frequent.

Tonic-clonic seizures (TCS), that is, generalized from its onset, tonic-clonic seizures (GTCS) and, focal to generalized, tonic-clonic seizures (FBTCS), are commonly associated with strong and sustained spasm of many body muscles along with respiratory arrest and tachycardia, leading to considerable metabolic stress.

Calculation of the serum anion gap has been used to detect errors in the measurement of serum electrolytes and to detect and evaluate metabolic acidosis

The current study proved that anion gap of a patient presenting with seizures can be a clue to differentiate its type either epileptic or psychogenic.

Serum bicarbonate level can also be used as distinguisher for type of seizures.

Current data indicate decreased ability of anion gap to differentiate with passage of time after attack of seizures, mostly after 2 hours of attack.

Limitations:

The studied groups were taken from one hospital that represent only small social category. Most patients were on antiepileptic medications thus it was not possible to prevent drug effect on anion gap levels.

Recommendation:

Taking into account, all the limitations of the study, Further studies with larger study groups are recommended to replicate, extend the current study findings and to achieve more adequate power to test the hypothesis and so that some insignificant correlations may prove to be significant.

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Nil.

Conflicts of interest:

There are no conflicts of interest.

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