Role of Creatine Kinase in Differentiating Tonic Clonic from Psychogenic Non-Epileptic Seizures in Emergency Department - Suez Canal University Hospital

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Abstract

Introduction: Psychogenic nonepileptic seizures are form of conversion disorder as paroxysmal episodes resembling epileptic seizures while lacking electroencephalogram correlation. Creatinine kinase (CK) is a muscle specific enzyme which may be useful marker for differentiation of psychogenic non epileptic seizures from generalized tonic colonic seizures. Aim: To assess the ability of serum levels of CK in differentiation between Generalized tonic-clonic seizures (GTCS) and Psychogenic nonepileptic seizures (PNES). Patients and methods: A prospective cohort study was conducted on 20 patients with GTCS and 20 patients with PNES who were presented in Suez Canal University Hospital. All patients were subjected to Initial assessment includes: History, clinical Examination, laboratory investigation, Radiographic: assessment. Serum CK in blood samples were drawn within 2 hrs., and 24 hrs. of the event from patients in both groups. Results: The current study found statistically significant older age with psychogenic non epileptic seizures compared to GTCS with p-value=0.037, 75% of patients with GTCS had positive EEG findings while only 10% of PNES had positive EEG findings, there was statistically significant higher CK level in GTCS compared to psychogenic non epileptic seizures with p-value <0.001. CK after 2h had 90% sensitivity, 85% specificity, AUC 0.926 at cutoff point 120 U/L and 90% sensitivity, 95% specificity, at cut off point 156 U/L for diagnosis of GNTS. Conclusion: Serum creatinine kinase can used in differentiation between psychogenic non epileptic seizures and generalized tonic colonic seizures, it had the advantage of continuous discharge even through 24 hours after seizures.

Key Words: Video electroencephalography, Reflex

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Introduction

Epilepsy is a disorder of the brain characterized by the predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition [(1)].

Seizure presented with abnormal, excessive, synchronous discharges of neurons residing primarily in cerebral cortex. it defined by any of the following conditions: (1) At least, two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome. A recent meta-analysis of 48 incidence studies estimated the pooled annual

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cumulative incidence of epilepsy as 67.77 per 100,000 persons (95% CI 56.6– 81.0) with one outlier report of 189.96 per 100,000 [3].

New onset seizure can be associated with infection, metabolic derangements, trauma, drug intoxication or withdrawal but most commonly is cryptogenic in origin. diagnosis implemented in the acute setting is often poorly discriminatory with conditions secondary to hypoglycemia,
hyponatremia or leukocytosis, although routine laboratory testing is often ordered [4].

Psychogenic nonepileptic seizures (PNES) are change in the behavior or consciousness similar to epileptic seizures but with psychological origin. PNES are categorized as a manifestation of dissociative or somatoform (conversion) disorders(5).

The clinical doubt of PNES depends on a precise description of the event by witnesses. Presence or absence of such physical signs as tongue bite or urinary incontinence may provide additional information to support or rule out the initial diagnostic suspicion [6–9].

The incidence of PNES was estimated to be 1.4–4.9/100,000/year and the prevalence was calculated to be between 2 and 33/100,000, making it a significant neuropsychiatric condition(10).

The differential diagnosis between PNES and epileptic seizures (ES) can represent a diagnostic challenge. Since they can be symptoms of a serious underlying condition, correct classification is essential for the subsequent diagnostic approach(11-13).

Misdiagnosis rates up to 20–30% are previously reported [13]. These patients have been on antiepileptic medications for years. This not only due to the needless healthcare costs but also the wrong diagnosis causes long-term adverse effects of anticonvulsant drugs, expense of therapy, and
above all social implications, which makes it essential for accurate diagnosis, before starting the treatment [14].

Video electroencephalography (EEG) recording represents the gold diagnostic standard in the differential diagnosis between PNES and ES [15,16]. However, patients with epilepsy can have normal EEGs, and patients without epilepsy may show EEG abnormalities [17]. Therefore, clinical findings with a detailed history and EEG combined with a rapid bedside diagnostic test would help minimize the diagnostic pitfalls [18].

Generalized tonic-clonic seizures (GTCS) are known to induce acute systemic increases in several plasma metabolites, enzymes, and hormones, such as prolactin, creatine kinase, cortisol, lactate, ammonium, and adrenocorticotropic hormone [14,19-22].

Laboratory markers aid the clinicians in determining whether an unwitnessed event was more probable to be epileptic or non-epileptic. Elevations in the creatine kinase (CK) levels are common after generalized tonic-clonic seizures (GTCS) and display high specificity and moderate sensitivity [23], it has been found to be elevated not long after a GTCS has occurred. Even days after a GTCS, CK can remain elevated [24].

CK begins to rise above normal limits within a few hours of the generalized tonic–clonic seizure and elevations are significant after 24 and 48h [25].

Serum CK have been traditionally studied to differentiate ES from PNES while the initial studies showed promising results; they were criticized for many weaknesses in the study design and revealed very limited studies considering serum CK as markers for differentiating epileptic and nonepileptic seizures [14].

Thus, the purpose of this study to assess the clinical value of measuring creatine kinase at presentation of patients with seizures and we looked at the ability of this readily available test to distinguish, individually and in combination, prospectively those patients who had a generalized tonic clonic seizure from those with psychogenic non epileptic seizure as determined by clinical presentation and appropriate investigations in Emergency Department in Suez Canal University Hospital.

Patients and Methods

This prospective Cohort study was conducted in Suez Canal University Hospital Emergency Department. It included 40 Patients (Based on that the mean in ictal group = 19.21 pg/ml μ2 = mean in non-ictal group = 7.05 pg/ml [14, 26] So, by calculation, the sample size was equal to 20 per group) presented with Tonic- Clonic Seizures (with suspected diagnosis of GTCS or PNES) in Suez Canal university teaching hospital emergency unit. All adult patients (>18 years) presented in the ED, patients presented with witnessed first ever either TCS or PNES within 2 hrs. of the event, both genders, the event was observed by witnesses such as, e.g., relatives or medical staff, and the time of the event before presentation was known were included. Patients younger than 18 years old, patients had an unclear history of seizure or PNES, patients known to have a recent trauma or strenuous activity, had suspicious acute coronary syndrome or ischemic ST-T wave changes on ECG, with comorbidities such as renal and endocrine disorders or any other condition known to elevate the creatine kinase, patients known to have a recent stroke, known pregnant women, history of drug use (such as narcotics), patients received Intramuscular injection within 7 days from the presentation (to exclude false elevation of creatine kinase), patients presenting after 2hrs from the start of event, or patients with positive CT findings (structural changes: brain tumor, history of head trauma, cerebrovascular accidents…). were excluded.

Data was collected in pre-organized data sheet by the researcher fulfilling inclusion and exclusion criteria. Every patient was assessed clinically and managed by using the ABCDE protocol. Over an 8-month period we prospectively identified patients with GTCS, who were brought to the hospital and examined neurologically within a few hours after the event. Each studied patient was subjected to the following:

- Detailed history taking: Personal data (name, age, sex, marital status, special habits), present
- history (full description of clinical features of the event to differentiate between true GTCS and PNES were obtained from family members, emergency room personnel or other observers and time of event: had to be a witnessed GTCS or PNES), chronic illness, past history (including detailed psychiatric history).
- Clinical examination: Vital signs, general examination and appearance, neurological examination. As by exam patients with ES was presented with abrupt onset, eye opening or widening at onset and post ictal confusion but patient with PNES was presented with preserved awareness, eye flutter, external effect can intensify or alleviate the fits.
- Laboratory investigations: CBC (Hb, TLC, PLT), electrolytes (serum sodium, serum potassium, and serum magnesium) were done on admission to rule out any comorbidities that could bias the study, LFT (Bilirubin: total/direct/indirect), ALT, AST, KFT (serum creatinine, blood urea nitrogen), CK (was measured within 2hrs of event and 24 hrs. later).
- Radiographic: Cerebral imaging (CT) to rule out any organic etiologies of the seizure, EEG (after 1-2 days from the attack of seizure), Chest X-ray, Electrocardiography was done.

Patients were categorized into either a PNES group or a GTCS group by the following criteria: "GTCS" group characterized by: a strange feeling or sensation "an aura", screaming or crying out involuntary at the beginning, losing control of your bladders and bowels, eye open, fixed unilateral head, bitten tongue, post ictal confusion, severe headache after the seizure, formed of "tonic stage": muscles stiffen and falling down, then "clonic stage": rapid muscle contraction, jerky movement, and tonic clonic seizures usually last 1-3 min **(27).**

PNES group characterized by: A trigger: light, sound is common, voluntary screaming is common, gradual onset, asynchronous movement of limbs, side to side head movement, eye closure, no tongue bite, urine incontinence is rare, alert, no post ictal confusion, last >2min [(28).]

Serum CK in blood samples were drawn within 2 hrs., and 24 hrs. of the event from patients in both groups. The two groups were compared and specificity and sensitivity of serum CK was determined as diagnostic markers for distinction between GTCS and PNES. finally, diagnosis was confirmed by EEG.

Statistical Analysis

- Statistical analysis was performed using statistical Package for the social sciences (SPSS) statistical program version 24.
- Significant difference in between 2 groups was calculated using t-test for parametric variables and Mann-Whitney U test for non-parametric variables. For 2 groups variables; unpaired t-test was used for parametric quantitative variables and Wilcoxon Signed-rank test was used for non-parametric quantitative variables. Between groups of qualitative data, chi-squared-test ($\chi 2$) was used.
- To identify relations between different variables, Pearson and Spearman correlation (r and ρ) were used.
- Results were considered to be statistically significant when P-value was less than 0.05.

Results

This prospective cohort study included patients presented with seizures in Suez Canal university teaching hospital emergency unit admitted to the Emergency department in Suez Canal University Hospitals. This study aimed to assess the ability of serum levels of CK can be used to differentiate GTCS and PNES activities, shows that patient with GTCS had comparable clinical measures compared to patients presented with psychogenic non epileptic seizures. Moreover, almost all patients in both groups were fully conscious at time of admission with GCS of 14 to 15 points as in table 1.

Table 2 shows that patients with GTCS had statistically significant higher ALT) compared to patients with PNES (17.35 ±2.519 vs15.45±2.625) (p=0.024).

Table 3 shows that patients with GTCS had significantly higher CK compared to patients with PNES at 2 hours after seizure (p<0.001), patients with GTCS had significantly higher CK compared to patients with PNES at 24 hours after seizure (p<0.001).

Table 4 shows the ROC curve analysis of CK at 2hrs for prediction of generalized tonic-clonic seizures, where the areas under the curve (AUC) were 0.926, for 2 hrs. CK, a value of 156 IU/L was found to be the best cut-off point for prediction of generalized tonic-clonic seizures among patients attending with seizures, with sensitivity = 90% and specificity = 95% and accuracy= 92.5%.

Table 5 shows that the ROC curve analysis of CK at 24 hrs. from the onset of the seizure for prediction of generalized tonic-clonic seizures, where the areas under the curve (AUC) were 0.913, for 24 hrs. CK, a value of 156 IU/L was found to be the best cut-off point for prediction of generalized tonic-clonic seizures among patients attending with seizures, with sensitivity = 90% and specificity = 95% and accuracy= 92.5%.

Discussion

Seizure is considered as the clinical expression of abnormal, excessive, synchronous discharges of neurons residing mainly in cerebral cortex. Epilepsy is a disease of the brain well-defined by any of: 1) at least, two unprovoked (or reflex) seizures occurring > 24 h apart; 2) one unprovoked (or reflex) seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; 3) diagnosis of an epilepsy syndrome [29].

Psychogenic non epileptic seizures are defined as change in behavior or consciousness resembling epileptic seizures but which have a psychogenic origin [28]. Video electroencephalogram (EEG) recording of an event is the gold standard for diagnosis [30].

This prospective cohort study was conducted on total number 40 patients, 20 of them with GTCS and the other 20 patients with PNES who were presented in Suez Canal University Hospital to assess the ability of serum levels of CK in differentiation between GTCS and PNES. Serum creatinine kinase have been traditionally studied to differentiate epileptic seizures from PNES [31].

The current study revealed statistically significant older age with psychogenic non epileptic seizures compared to GTCS with p-value=0.037. This goes in run with another Egyptian study by Fawi et al. which was conducted on 20 epileptic patients and 20 with psychogenic non epileptic seizures to establish other diagnostic methods that are accurate as video EEG for differentiation and revealed that PNES occurred mostly with older age compared with epileptic seizures with p-value<0.01 (32).

In contrast to Jaramillo-Jimenez study which revealed no statistically significant difference between GTCS and PNES as regards age with p-value =0.298 [33].

The current study found no statistically significant gender difference was reported between generalized tonic colonic and PNES with p-value>0.05.

Our study found no statistically significant difference between GTCS and PNES as regards serum Na and K levels with p-value >0.05. In contrast to Priyanka Parihar et al. study which found statistically significant lower Na level in GTCS compared to PNES, while there was no statistically significant difference between GTCS and PNES as regards K level. The active pumping of positively charged sodium ions out of the cell makes the nerve cells between discharges to have a negative charge internally. Discharge or firing of the nerve cell involves a sudden fluctuation of the negative charge to a positive charge as ions channels into the cell open and positive ions, such as sodium, potassium, and calcium, flow into the cell. Both excitatory and inhibitory control mechanisms act to allow appropriate firing and prevent inappropriate excitation of the cell [34].

Sodium is the major extracellular cation. A loss of sodium from body results in a decrease of extracellular fluid volume affecting circulation, renal function and nervous system. Complications of rapid and severe growing hyponatremia contain seizures, generally generalized tonic–clonic. Seizures generally occur if the plasma sodium concentration rapidly decreases to <115 mEq/L; they represent an ominous sign and also medical emergency, as they are associated with high mortality **[35].**

The decreased levels of Sodium in GTCS patients were observed statistically highly significant (p<0.0001) when compared with healthy controls while in PNES the decrease was statistically non-significant **[34].**

Potassium is major intracellular cation. Its concentration in plasma determines neuromuscular & muscular irritability. Unlike other electrolyte alterations, hypokalemia or hyperkalemia rarely causes symptoms in the CNS nor seizures. Changes in the extracellular potassium level (serum levels) have major and deep effects on the neuromuscular and cardiovascular systems function. Thus, severe potassium abnormality may provoke fatal arrhythmias or muscle paralysis before CNS symptoms appear **[35].**

Increase or decrease in potassium levels can cause muscle weakness, muscle cramps, muscle twitching, low blood pressure, respiratory failure, paralysis and the muscle breakdown disorder called rhabdomyolysis; but seizures rarely occur. The decreased levels of potassium in GTCS and PNES patients was observed statistically non-significant when compared with healthy controls(34).

As regards EEG in our study, 75% of patients with GTCS had positive EEG findings while only 10% of PNES had positive EEG findings. Another study by Faulkner which aimed to examine the utility of alternate investigation of outpatient ambulatory EEG and revealed that of 64 patients with picture of epilepsy; EEG results detected in 70% of epileptic seizures and in 23% of PNES [36]. Matching with our study, another study by Reuber et al. reported that EEG of patients with seizures; 92.9% had picture of PNES and epilepsy, while 53.8% of PNES group had one or more of abnormal EEG findings [37].

Our study found statistically significant higher CK level in GTCS compared to psychogenic non epileptic seizures with p-value <0.001. this goes in run with Petramfar et al. study which was conducted on 20 patients with GTCS, 20 PNES and found statistically significant elevation of CK in GTCS compared to PNES with p value=0.0001(38). Another study by Javali et al. reported elevated CK in 91.66% of GTCS compared to 9% of PNES [39]. A previous systemic meta-analysis by Brigo et al. had found that serum CK had sensitivity ranged from 14.6% to 87.5%, and specificity ranged between 85 to 100% for diagnosis of epileptic seizures [40].

Another study by Ijaz et al. which was conducted on 30 patients with GTCS, 30 patients with pseudo seizures and 30 healthy subjects and revealed that serum CK was significantly elevated in epileptic group compared to pseudo-seizure group with p-value <0.05, which can be explained by severe muscular contractions with epileptic seizures [41]. Nass et al. previously assessed frequency of complications occurring in association with GTCS and found that CK was increased in 59.4% of GTCS patients, with <5-fold increase in 47%, <10 fold increased in 5.8%, and > 10-fold increase in 4.3% [42]. Libman et al. stated that if sampling serum of CK has done at least 3 hours postictally, it is proved to have high specificity of serum CK from detecting generalized seizures with enhanced sensitivity [43]. Increased CK appears to point towards an increased risk of severe rhabdomyolysis **[42].**

Assessment of serum creatinine beyond 24-48 h might detect normal levels (risk of false negative results), while the progressive elevation of CK over time can be helpful in differentiation of seizures related elevated CK. As Holtkamp et al. study which included patients with refractory generalized convulsive status epilepticus and revealed that only one patient with normal CK in first 24h showed a marked increase of CK 40h after seizure onset **[44].**

Our study found that CK after 2h had 90% sensitivity, 85% specificity, area under ROC curve (AUC) 0.926 at cutoff point 120 U/L and 90% sensitivity, 95% specificity, at cut off point 156 U/L for diagnosis of GTCS. Matching with Petramfar et al. study in which CK had sensitivity 75% and specificity 86% for diagnosis of GTCS**(38).**

Conclusion

In conclusion, Serum creatinine kinase can used in differentiation between psychogenic non epileptic seizures and generalized tonic colonic seizures, it had the advantage of continuous discharge even through 24 hours after seizures.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Ethical approval

The current study complies with national and international guidelines. The current study was approved by the research ethics committee at Suez Canal university Code No: R/78. The participants gave informed written consent to participate in the study. Laboratory results were given to all tested members. All results were used for research purposes only. All data was saved, only the researcher had access to it. No stored samples were shipped out of the country. The subjects had the right to withdraw samples at any time.

Authors, contribution

All authors are equally contributed.

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Tables and graphs

Table 1: Clinical characteristics of the studied group.

Variables	Groups GTCS (n= 20)	PNES (n= 20)	P-value
Clinical parameters Systolic blood pressure (mmHg)	130.0 ±14.142	122.50 ±10.195	0.086 a
Diastolic blood pressure (mmHg)	86.00 ±9.403	82.50 ±8.507	0.213 a
Pulse (beat/min.)	77.60 ±9.081	73.20 ±5.559	0.121 a
Respiratory rate (cycle/min.)	18.05 ±1.504	17.55 ±1.191	0.367
GCS 14	3 (15)	0 (0)	
			0.075 b
15	17 (85)	20 (100)	

a p-values are based on independent t- test. Statistical significance at P < 0.05 b p-values are based on Chi square test. Statistical significance at P < 0.05

Table 2: Laboratory data of the study groups.

Variables	Groups	
GTCS (n= 20)	PNES (n= 20)	p-value

Laboratory measures Hemoglobin (g/ dl) ±1.370	12.935 ±1.625	12.575	0.512
TLC ±2619.4	6885.5 ±2860.4	7685.0	0.279
Na^+ ±3.00	139.80 ±1.64	139.4	0.417
K^+ 0.38	3.990 ±0.53	3.845 ±	0.437
ALT (IU/ L) ±2.625	17.35 ±2.519	15.45	0.024*
AST (IU/ L) ±1.429	17.90 ±2.918	16.60	0.084
Creatinine (mg/ dl) ±0.2269	0.680 ±0.1735	0.690	1.000

[a] p-values are based on independent t- test. Statistical significance at P < 0.05

Table 3: Comparison of 2-hour CK and 24-hour CK between GTCS and PNES groups.

Variables	GTCS	PNES	p-value
	(n= 20)	(n= 20)	
Creatine kinase (CK)			
After 2 hrs.	250.65 ± 85.581	95.75 ± 60.258	<0.001*
After 24 hrs.	284.00 ± 106.484	87.80 ± 42.785	<0.001*

[a] p-values are based on Mann Whitney test. Statistical significance at P < 0.05

Table 4: Sensitivity, specificity, PPV, NPV and diagnostic accuracy at different cut off levels of CK at 2hrs for prediction of generalized tonic-clonic seizures.

Variable	Area	Stand. error	p-value	95% CI	
2 hrs. CK	0.926	0.046	<0.001*	(0.836 – 1.000)	
Cut-off points	Sensitivity	Specificity	PPV*	NPV*	accuracy
2 hrs. CK					
112 U/L	90%	70%	72%	86.7%	77.5%
120 U/L	90%	85%	85.7%	89.5%	87.5%
156 U/L	90%	95%	94.7%	90.5%	92.5%
188 U/L	85%	95%	94.4%	86.4%	90%
193 U/L	80%	95%	94.4%	82.6%	87.5%

Table 5: Sensitivity, specificity, PPV, NPV and diagnostic accuracy at different cut-off levels of CK at 24 hrs for prediction of generalized tonic-clonic seizures.

Variable	Area	Stand. error	p-value	95% CI	
24 hrs. CK	0.913	0.058	<0.001*	(0.799 – 1.000)	
Cut-off points	Sensitivity	Specificity	PPV*	NPV*	accuracy
24 hrs. CK					
110 U/L	90%	80%	78.3%	88.2%	82.5%

112 U/L	90%	85%	85.7%	89.5%	87.5%
156 U/L	90 %	95 %	94.7%	90.5%	92.5%
212 U/L	85 %	95 %	94.4%	86.4%	90%
233 U/L	90%	75%	78.3%	88.2%	82.5%