E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.31838/ijprt/15.02.480

Research Article

Role of Creatine Phosphokinase in Differentiating Epileptic Seizures and Psychogenic Non Epileptic Seizures

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Received: 10.10.25, Revised: 16.11.25, Accepted: 04.12.25

ABSTRACT
Background: A seizure is an excessive abnormal hyper synchronous activity in the brain. Psychogenic Non epileptic seizures (PNES) are paroxysmal events that resemble seizures but are not associated with abnormal cortical activity and have a psychological origin. Multidisciplinary evaluation with video EEG even though diagnostic for these conditions; limitations in the availability and lack of changes in scalp EEG in all epileptic seizures might lead to misdiagnosis translating into inappropriate anticonvulsant therapy. Estimation of biomarkers like Creatine Phosphokinase (CPK) could be a readily available and cost-effective alternative. The objective was to determine the sensitivity and specificity of Creatine Phosphokinase in differentiating epileptic seizures from psychogenic non epileptic seizures in a patient presenting with new onset seizures.
Methodology: All patients presenting with new onset seizures in Department of General Medicine ward and casualty of Government Medical College, Kottayam were included in the study conducted over a period of 12 months. The patients were diagnosed with epileptic seizures or PNES using targeted investigations. The CPK levels were estimated and correlated with the diagnosis.
Results: Of the 60 participants, 43 (71.7%) presented with epileptic seizures and 17(28.3%) presented with PNES. There was a significant association of elevated mean CPK levels with epileptic seizures compared to PNES (1118±967.62 versus 172.23± 71.56). CPK had a sensitivity of 100% and specificity of52.94% in differentiating epileptic seizures and PNES.
Conclusion: Creatinine Phosphokinase can be considered as a biomarker with excellent sensitivity in differentiating epileptic seizures and PNES.

Keywords: Seizure, Psychogenic Non Epileptic Seizure, Creatine Phosphokinase.

INTRODUCTION

Epilepsy is diagnosed when there is a risk of recurrent seizures due to a chronic underlying process. Seizures can be epileptic or non-epileptic. Non epileptic seizures can be Physiologic or Psychogenic. Psychogenic Non-Epileptic Seizures (PNES) pose considerable challenges to the health care workers by causing paroxysmal events arising from a psychogenic cause. This results in alterations in behavior, experience, sensation, or movement, however there is no ictal epileptiform activity.[1]While patients on long term follow up for monitoring epilepsy would be diagnosed in as high as 40% eventually, those with long standing PNES could develop epilepsy in 10-15%.[2] The video electroencephalography (vEEG) is considered the best diagnostic option in distinguishing epileptic seizure(ES) from PNES.[3] The coexistence of the ES and PNES, absence of biological or psychological markers with good specificity, the high expense and lack of availability of the gold standard vEEG at primary and secondary health care centres necessitates the evaluation of potential bio markers that can differentiate between the two. Even though several post ictal biomarkers have been studied in this context, the data from the Indian context on markers is still insufficient. The objective of this study was to determine the sensitivity and specificity of Creatine Phosphokinase in differentiating epileptic seizures from psychogenic non epileptic seizures in a patient presenting with new onset seizures.

METHODOLOGY

This was a cross-sectional study done for a period of 12 months from January 2023-2024 in the department of general medicine of

Government Medical College in Central Kerala (IRB 39/2023 dated 13.01.2023). All patients presenting to the medicine casualty with new onset seizures fulfilling the inclusion criteria of any gender patient above 18 years with new onset seizures were included through consecutive sampling till the calculated sample size was reached. The sample size was estimated to be 60 based on a study by Javeli et al using the formula $2 \times (Z\alpha + Z\beta)2(SD)2/M2$ where SD=SD1+SD2/2 (SD1=195.8. SD2=23.6) and M=M1-M2(M1=256.2, M2=57.94).[4]Patients with previous history of seizures, diagnosed ES or PNES, those with syncope, presenting after 12 hours of seizure onset, known cases of musculoskeletal, renal or endocrine diseases, pregnant ladies and patients on statins, antipsychotics or drugs interfering with CPK values were excluded from the study. The data including medical history and physical examination. routine investigations, CPK values, CT Brain and EEG reports were collected in a structured proforma. Serum CPK levels were measured at 12 hours post seizure using a modification of ultra violet enzymatic determination. A cut off of 160 U/L was taken as normal. The data were entered in Microsoft Excel and analysed using IBM SPSS Statistics for Windows Version 20.0. Armonk, NY; IBM Corp.

RESULTS

A total of 60 patients, 30 males and females with new onset seizures were included in the study Forty three participants were diagnosed with epileptic seizure 23(53.4%) males and 20(46.6%) females. Of the seventeen participants diagnosed as PNES 7(41.1%) were males and the rest 10(58.8%) females. As shown in Figure 1 the most number of Epileptic seizures were in the age group 51-60 and 71-80 years 8(18.6%). The number of PNES were equal in age groups 21-30, 31-40 and 41-50 years at 4(23.5%).

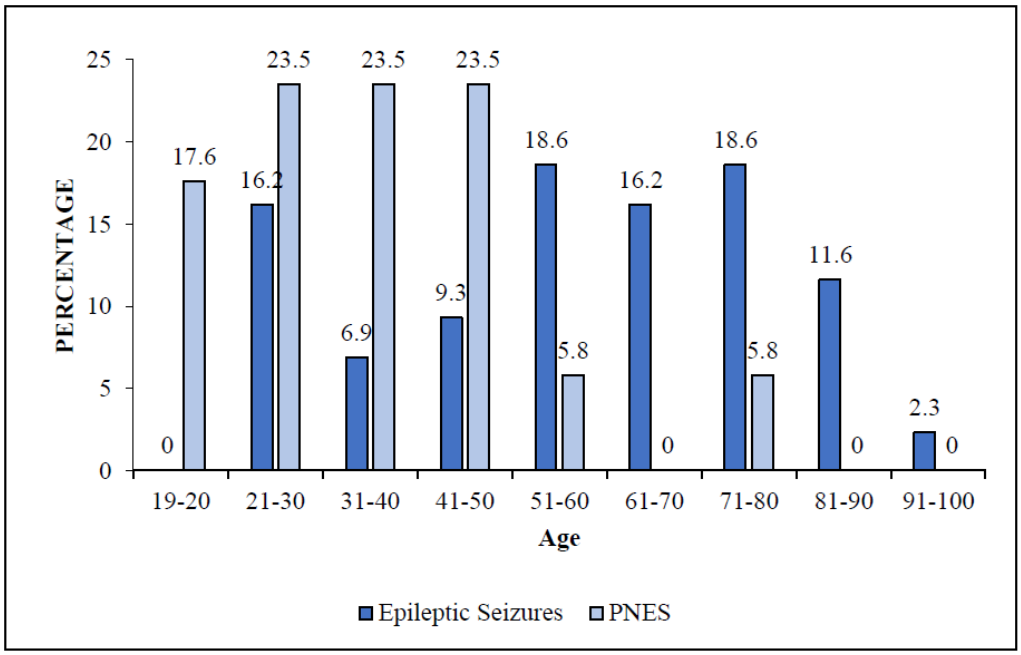

Fig 1: Age Distribution of the Participants

Among the 43 participants who presented with ES 16 had focal seizures and 27 had Generalised Tonic Clonic Seizures (GTCS). Table 1 shows the frequencies of seizure episode in the participants. Of the 60 participants, majority had a single episode of ES 23(53.4%) while two participant had 5 episodes of ES. Eight participants had 2 PNES and one had upto 5.

Table 1: Frequency of Seizure

Frequency Of Seizure	Epileptic Seizures	Psychogenic Non Epileptic Seizures
1	23 (53.4%)	4 (23.5%)
2	15 (34.8%	8 (47%)
3	2 (4.6%)	0

4	1 (2.3%)	4 (23.5%)
5	2 (4.6%)	1 (5.8%)

As shown in Figure 2, majority of the participants 16 (37.2%) and 7 (41.1%) presented to casualty after two hours, however 1 patient each in ES and PNES came to the casualty only after10 hours. As depicted in Fig 3, the major cause of epileptic seizure was metabolic 16(37%).

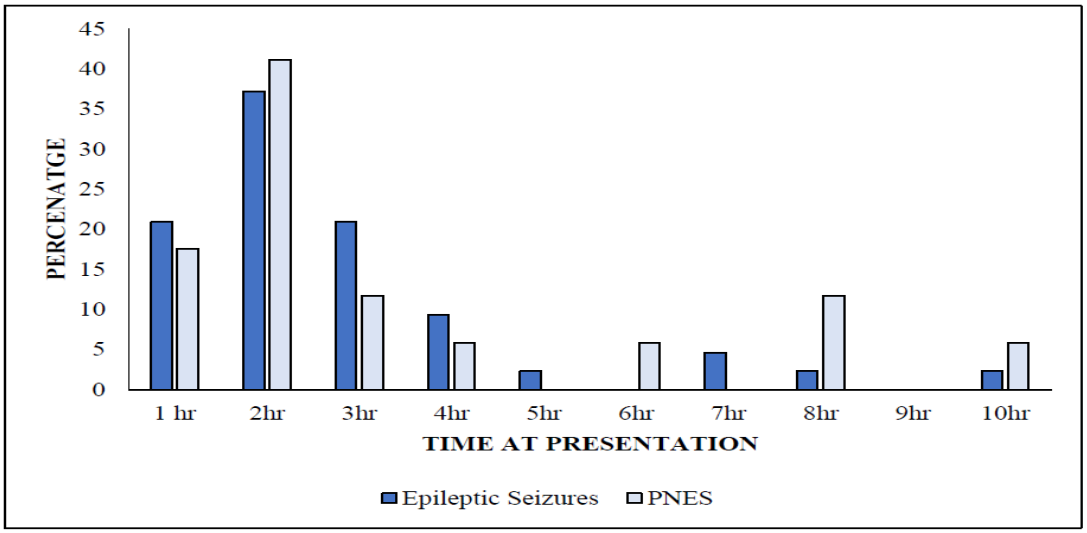

Fig 2: Timeline of Patient Presentation in the Casualty after Seizure Episode

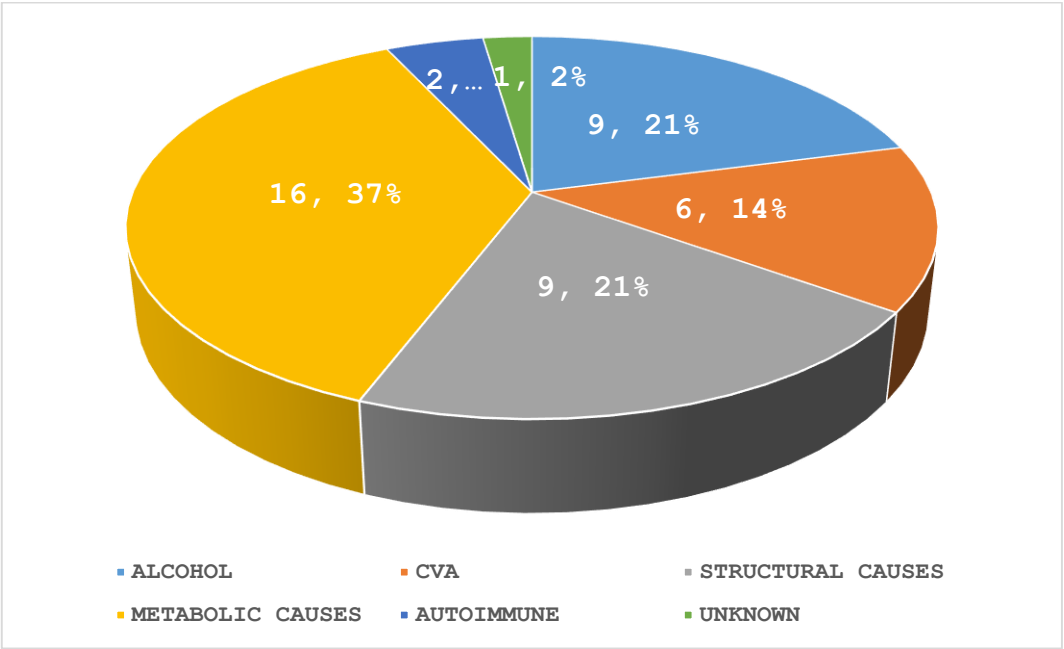

Fig 3: Etiology of Seizure Episodes

The mean CPK values in Epileptic seizures was 1118.23 ±967.62 and 172.23±71.56 with a p value of < 0.001 indicating statistical significance. The mean CPK values in Focal and GTCS were 992.75 and 1192.5 respectively. As shown in Fig 4, the mean CPK levels were highest in seizures following cerebrovascular accidents (CVA) and lowest in those with an aetiology of alcoholism.

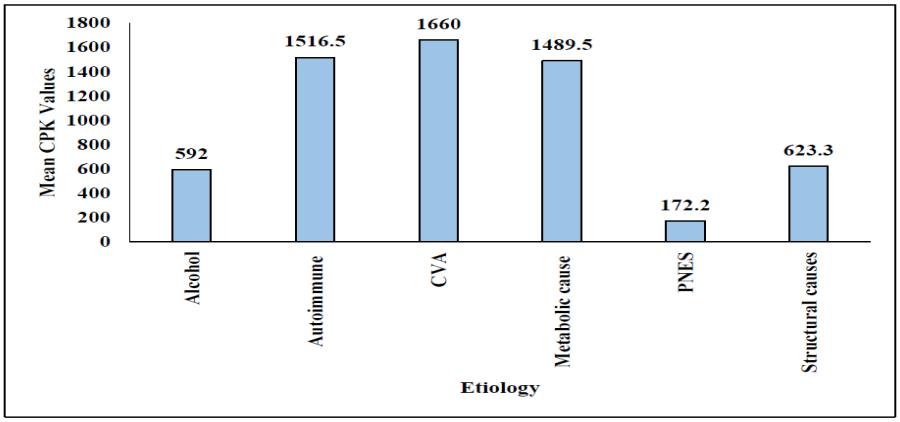

Fig 4: Mean CPK Based On Aetiology

As summarized in Table 2, the mean CPK values were highest at 1405.5± 260.92 when there were 3 episodes and lowest for a number of 4 seizures at 677. The highest CPK values were for 5 episodes of PNES 221 and lowest for 2 episodes of PNES 156.75. Figure 5, depicts the scatter plot of the CPK values of each participant.

Table 2: Mean CPK Based On Frequency of Seizures

Frequency Of Seizure	Epileptic Seizures	Psychogenic Non Epileptic Seizures
1	1048.52±755.61	166.75±65.19
2	1183.86±1310.97	156.75±40.13
3	1405.5±260.92	0
4	677	196.5± 130.56
5	1361±1407.14	221

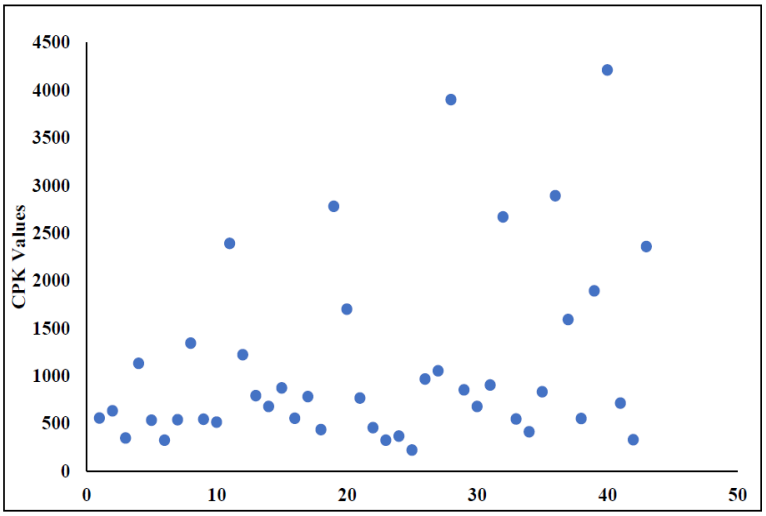

Fig 5: Scatter Plot of CPK Values

Table 3: Sensitivity and Specificity of CPK

Diagnosis	Number of Patients above CPK cut off	Number of Patients below CPK cut off
ES	43	0
PNES	8	9

ES-Epileptic Seizure PNES-Psychogenic Non Epileptic Seizure

Based on table 3, the sensitivity was estimated to be (43/43) *100=100% and the specificity was (9/17) *100=52.94%. This result was similar for the GTCS (n=27) and Focal seizure(n=16) as CPK was elevated in all the participants with ES.

DISCUSSION

This study included 60 patients with new onset seizures of which 43 had ES and 17 had PNES. While ES was more in males, there was a higher incidence of PNES in the females. There were equal number of males and females in this study as compared to that by Javali et al., in which 55.9 % of the total participants were males and 44.1 % were females.[4] The mean age of participants was 51.18 ±10.73 while it was 42.24 years in another study.[4]

Several biomarkers have been identified in epilepsy like brain derived biomarkers like ubiquitin C-terminal hydrolase 1 (UCHL-1), metalloproteinase 9 (MMP-9) abundant in neural tissues, microtubule-associated protein tau (Tau), neuronal specific enolase (NSE), glial fibrillary acidic protein (GFAP),neurofilament light protein (NfL), and S100 calcium-binding protein B (S100B).[5]

Neuroinflammatory biomarkers like cytokines IL 1β, IL2 and IL4 have been studied in reference to seizure biomarkers.[6] IFN γ and TNF α have also been found to be elevated in seizures.[7]Brain Derived Neurotrophic Factors and plasma NT3, CTNF, and NGF levels have been found to be elevated in recent exploratory studies.[8,9] Creatine kinase (CK) and lactate and lactate are blood biomarkers that are elevated in seizures. CK rises within the first 1-2 hours and peaks 24–72 hours later in GTCS whereas after focal convulsions it is found to increase after 24 hours and in absence seizures, SPS, or CPS it doesn't rise.[10]

The mean CPK values among participants with Epileptic seizures was 1118±967.62 and among participants with PNES was 172.23÷71.56. All the participants with Epileptic seizures had a CPK value more than cutoff while 47% of participants with PNES had a CPK value more than cutoff and 52.94% had a CPK value less than cutoff. In the study by Javali et al, 91.66% of patients with GTCS had elevated CPK while 70% with partial seizures had elevated CPK.[4] None of the patients with PNES had elevated levels. CPK levels were estimated at 1 hour post seizure by Javal et al., while in this study, seizures presenting before 12 hours were included. In a study by Libman et al, improved sensitivity for CPK levels was found at least 3 hours postictally and Neufeld et al found that a high increase in CPK values occurs in the 2nd day after seizure and that an increase of at least 15 U/L is highly indicative of an epileptic event.[11]

While Javali et al showed that CPK is a biomarker with high specificity and low sensitivity, this study gives a sensitivity of 100% with a specificity of 52.94%. In a study by Petramfar et al, CPK concentrations were above cut off of 160 mg/dl in 75% of patients with GTCS, 15% of patients with PNES, 13.6% with Vasovagal syncope and 15% of control group.[12] The sensitivity of postictal CPK for ES ranged from 14.6 to 87.5% and specificity ranged from 85 to 100.[13] In a meta analysis by Abdelnaby et al, subgroup analysis of CPK levels showed it was higher in patients below 40 years of age, and showed variability according to nationality with highest values in Switzerland. CPK levels also varied according to method of analysis with highest values with a random kit and lowest with an automatic analyser. There was also higher levels of CPK in emergency room studies as compared to in research studies, this was attributed to other factors like possible falls and injuries, IM injections and drugs like alcohol.[14]

In this study 20.9% of seizures had alcohol as an etiology. CPK levels were also found to be more prolonged in prolonged seizures and serial seizures. In this study, CPK values had differences depending on etiology of seizure and number of seizures. Mean CPK values were highest in seizures due to CVA and lowest in seizures due to Alcohol. In Mean CPK values depending on number of seizures, CPK did not rise with increasing number of seizures. In a prospective study by Goksu et al. in differentiating seizure and syncope there was no statistical significance for the first samples but the samples drawn at 4 hours was found to be significantly higher in favour of seizure group ($P < 0.05$). Sensitivity and specificity for CPK was 34% and 89% respectively at 4 hours.[15]In a prospective study by Willert et al. to evaluate the discriminative power of CPK in ES and PNES, measurement of markers were done in 44 single seizures with continuous video- EEG monitoring, it was found that sensitivity of prolactin was found to be higher than CPK but CPK had higher positive predictive value.[16]

The limitations of the study include the referral bias this being a tertiary centre, the involvement of CPK rise influenced by various other factors like presence of fall or injury, drugs like alcohol and intramuscular injections.

CONCLUSION

Creatine Phosphokinase has a Sensitivity of 100% and Specificity of 52.94% in differentiating Epileptic Seizures from PNES. The results highlight the variability in CPK according to the number, type and etiology of seizures. Exploring the relationship between

CPK and seizures can offer faster and cheaper alternatives to differentiate seizures from alternative diagnosis. Due to the study's limitations, which include possible measurement variability and single site design, bigger multicentric investigations are needed to better understand the relationship between CPK and seizures.

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