



## Role of Inflammation and Serum Creatine Phospho Kinase in Seizures

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### ABSTRACT

**Background and Objectives:** Epilepsy which is a disorder with an extensive variability of symptomatology and multifactorial origins is categorized by emergent and recurrent seizures. Numerous studies showed that seizures are triggered by hyperactivity of the neurons of the brain which may be atypical and synchronous. Our study was aimed to find out the association of inflammation in terms of total leukocyte count (TLC) and serum creatine phosphokinase (CPK) concentration in epilepsy and their comparison with pseudo-seizures and healthy controls. **Methodology:** We conducted this study in Mayo Hospital, Lahore with the collaboration of the Physiology Department of King Edward Medical University, Lahore after approval from Advanced Studies and Research Board of KEMU, Lahore. The sample size was ninety and they were divided equally into three groups, 30 patients of GTCS, 30 patients with a history of pseudoseizures and 30 healthy subjects of comparable age.  $p < 0.001$  was taken as significant. Statistical analyses were done using SPSS 21. **Results:** Mean total leukocyte count (TLC) in Pseudo-seizures groups was  $8216.3 \pm 2195.8$  cu.mm, in the epileptic group was  $13219.9 \pm 2686.8$  cu.mm and in the control group, the mean TLC was  $6832.1 \pm 1154.9$  cu.mm. Mean serum CPK in pseudo-seizure groups was  $130.1 \pm 74.3$  IU/100 ml, in the epileptic group was  $257.7 \pm 24.6$  IU/100 ml and in the control group, the mean CPK was  $79.9 \pm 27.7$  IU/100 ml. **Conclusion:** Total leukocyte count (TLC) and CPK were higher in the epileptic group as compare to the pseudo-seizure groups as well as the control group. Elevated WBC levels may be a result of continuing inflammatory progressions in the pathogenesis of epilepsy. Therefore it was concluded that serum CPK and TLC may serve as a differentiating marker between epileptic generalized tonic-clonic seizures (GTCS) and pseudo seizers.

**Keywords:** Total leukocyte count, Serum creatine phosphokinase, Epilepsy

### INTRODUCTION

Epilepsy which is a disorder with an extensive variability of symptomatology and multifactorial origins is categorized by emergent and recurrent seizures. Numerous studies showed that seizures are triggered by hyperactivity of the neurons of the brain which may be atypical and synchronous [1]. Worldwide 1%-3% population is affected by epilepsy [1,2]. Augmented excitability of the brain nerve cells due to cerebral dysfunction may be the presentation of epilepsy. Epilepsy displays a stereotyped syndrome of awareness, conduct, moods, and insights in a definite period that are produced by enlarged, fast electrical ejections of grey matter [3]. Even though the exact etiology of epilepsy is still unknown, primary mechanisms stress on vascular cerebral disease, shock, and neoplasms [4-6]. Various conditions of inflammation, the situation of clinical status and prompting factors connected to these diseases may be linked with epilepsy. Recent studies focused on the role of brain tissue inflammatory mechanisms in the genesis of epilepsy [7,8]. The role of inflammation in epilepsy is further proved by records acquired from experimental representations and tissue of the human brain [9]. It is documented that Chemokines are liable for the uptake of leukocytes in epileptic brains as a result of neuroinflammation [10]. Fresh studies recommended a prognostic worth and a strong relationship of the ratio of neutrophils and lymphocytes in inflammatory conditions such as cardiovascular diseases, smoking and solid tumors [11]. It is believed that long-standing inflammation can encourage hyper-excitation of the brain and may

result in recurrent seizures. Various biomarkers have been identified which are recommended to discriminate types of various seizures and in turn develop substitute therapies. We can say that as more evidence regarding the inflammatory role in disease advancement increases, the focus will be shifted towards the possible use of disease altering remedy for the creation of precise anti-inflammatory drugs and new treatment methodologies [12]. Creatine kinase is thought to play an important role in the metabolism of cellular energy. It is usually found in great concentrations in metabolically active cells like skeletal muscles and neurons [13]. However, it is very difficult to prove the actual role of creatine phosphokinase in non-epileptic seizures [14].

It is normally supposed that leucocytosis may be induced by status epilepticus and to certain grade generalized tonic-clonic seizures [15]. Nonetheless, any prospective study assessing the association of leukocyte count to an alone seizure could not be found. It is to be noted that the reason for this rise in the leukocyte count is neither well understood nor studied in detail. The count of White blood cells normally increases after strenuous exercise [16]. Muscular actions during the seizure may lead to the rise of white blood cell count following a seizure. Raise in WBC count may be directly linked to the duration of the activity of generalized tonic-clonic seizures. It is very important to properly distinguish epileptic generalized tonic-clonic seizures (GTCS) from either psychogenic nonepileptic seizures (PNES) or vasovagal syncope (VVS). Therefore the current study was aimed to find out the association of inflammation in terms of total leukocyte count and serum CPK concentration in epilepsy types and their comparison with healthy controls.

## METHODOLOGY

We conducted this study in Mayo Hospital, Lahore with the collaboration of the Physiology Department of King Edward Medical University, Lahore after approval from Advanced Studies and Research Board of KEMU, Lahore. Written consent was obtained from the subjects and their guardians at the spot. Ninety female subjects were enrolled in our study and they were divided into three groups, each of which comprised of 30 subjects: Group 1: Patient with a confirmed previous history of grand mal seizures and including freshly diagnosed cases of GTCS (n=30). Group 2: Patient with a history of pseudoseizures (n=30). Group 3: Control group: Females of comparable age (n=30). Young females of childbearing age of 16 to 35 years, having a history of seizures were included in our study. We excluded patients with a history of Head Trauma, Brain tumour, Meningitis, Cerebrovascular accidents, metabolic disorders (Hypoglycaemia, hypocalcemia), Muscle injuries and mental impairment. Pregnant and lactating females were also excluded from the study. A blood sample of 5 ml within 30 minutes of a seizure or pseudo seizure was collected. The samples were sent to the center of nuclear medicine (CENUM) of Mayo Hospital, and the pathology department of King Edward Medical University Lahore for processing within 24 hours. Serum creatine phosphokinase (CPK) was measured by randox kit using Biochemical Analyser (Model AE600N). Leucocytosis was considered for a WBC count of above 12,000 cells/mm<sup>3</sup> in patients. Statistical evaluation was done using Statistical Package for the Social Sciences for Windows 16.0 (SPSS Inc., Chicago, IL, USA). Results were presented as the Mean  $\pm$  Standard Deviation (SD). Statistical analyses were done using SPSS 21. ANOVA was used to compare the results of the different groups. Statistical significance was set at  $p < 0.001$ .

## RESULTS

The mean ages of females included in control, pseudo-seizure and the epileptic group were  $23.4 \pm 4.7$  years,  $21.9 \pm 5.5$  year and  $21.6 \pm 4.1$  years respectively. The age limit in all females was 16 to 35 years. The mean age in both the pseudo-seizure group and epileptic group was not significantly different ( $p=0.792$ ) but was lower than the control group without significant difference ( $p= 0.25$  and  $0.098$  respectively).

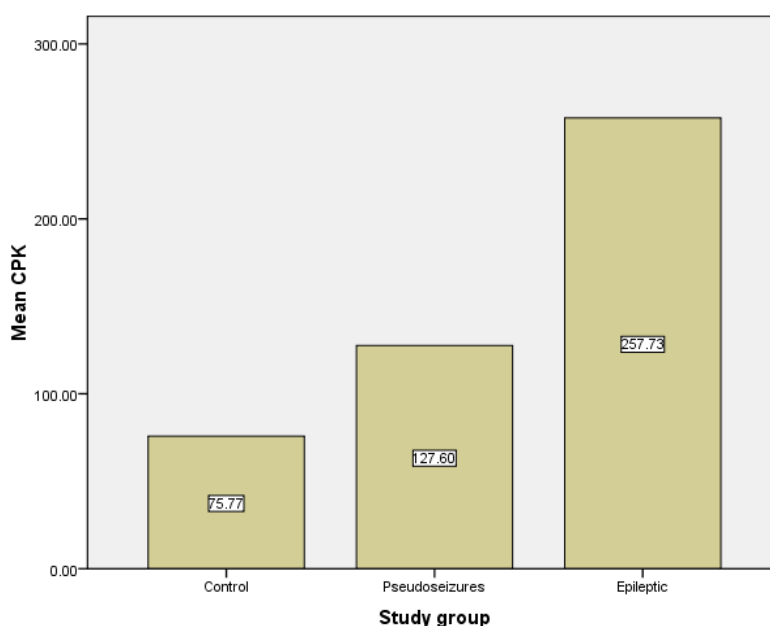
Mean serum CPK in pseudo-seizure groups was  $130.1 \pm 74.3$  IU/100 ml, in the epileptic group was  $257.7 \pm 24.6$  IU/100 ml and in the control group, the mean CPK was  $79.9 \pm 27.7$  IU/100 ml. On applying ANOVA we found a significant difference between the levels of CPK among three groups, on further investigations we found that serum CPK was higher in the epileptic group as compared to pseudo-seizures groups and control ( $p < 0.001$ ) and CPK was also higher in pseudo-seizures when compared to control group ( $p < 0.001$ ). This is shown in Table 1 and graphically depicted (Figure 1).

The mean total leukocyte count (TLC) in Pseudo-seizures groups was  $8216.3 \pm 2195.8$  cu.mm, in the epileptic group was  $13219.9 \pm 2686.8$  cu.mm and in the control group, the mean TLC was  $6832.1 \pm 1154.9$  cu.mm. On applying ANOVA we found a significant difference between the values of TLC among three groups, on further investigations, we found that TLC was higher in the epileptic group as compared to pseudo-seizures groups and control ( $p < 0.001$ ) and TLC was also higher in pseudo-seizures when compared to control group,  $p < 0.001$ . TLC figures are shown in Table 2 and a graph (Figure 2).

**Table 1 Pairwise comparison of serum CPK among different groups**

Variable	Study Group		p-value
CPK (IU/100 ml)	Pseudo-seizure ( $130.1 \pm 74.3$ )	Epileptic ( $257 \pm 24.6$ )	0.00001
		Control ( $79.9 \pm 27.7$ )	0.001
	Epileptic ( $257 \pm 24.6$ )	Pseudo-seizure ( $130.1 \pm 74.3$ )	0.00001
		Control ( $79.9 \pm 27.7$ )	0.00001

\*Significant ( $p < 0.05$ )

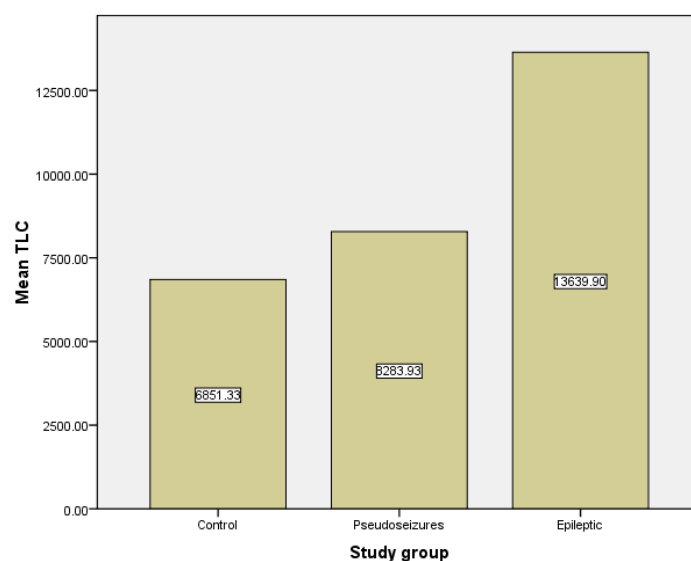


**Figure 1 Comparison of Mean Serum CPK in study groups**

**Table 2 Pairwise comparison of TLC among different groups**

Variable	Study Group		p-value
TLC	Pseudo-seizure ( $8216.3 \pm 2195.8$ cu.mm)	Epileptic ( $13219.9 \pm 2686.8$ cu.mm)	0.0001
		Control ( $6832.1 \pm 1154.9$ cu.mm)	0.003
	Epileptic ( $13219.9 \pm 2686.8$ cu.mm)	Pseudo-seizure ( $8216.3 \pm 2195.8$ cu.mm)	0.0001
		Control ( $6832.1 \pm 1154.9$ cu.mm)	0.0001

\*Significant ( $p < 0.05$ )



**Figure 2 Comparison of TLC in study groups**

## DISCUSSION

We in this study determined serum levels of CPK and TLC as a marker of inflammation in epileptic and psychogenic non-epileptic seizures and compared their mean with healthy controls. The mean CPK level in our patients was 257 U/100 ml in the epileptic group which was significantly elevated after epileptic seizures due to severe muscular contraction. But on the other hand, the mean CPK level was 127.60 U/100 ml in the pseudo-seizure group which was quite low as compared to the epileptic group but this figure is slightly higher as compared to the control group in which the mean CPK value was 70.77 U/100 ml. Thus, CPK was higher in the epileptic group as compared to the pseudo-seizure groups as well as the control group. The reason may be that in epileptic as well as in pseudo-epileptic patients there may be some sort of muscular damage due to severe muscular contraction responsible for the release of CPK in blood. In a previous study done by Petramfar, et al., mean CPK concentrations were significantly higher in patients of GTCS, in which serum CPK concentrations had 75% sensitivity and 86% specificity for the conclusion of GTCS. In that study, the levels of CPK were found beyond 160 ml/dl in 75% of the patients of GTCS [17].

Libman, et al., earlier stated about if sampling serum has done at least 3 hours postictally, it is proved to have high specificity of serum CK for detecting generalized seizures with enhanced sensitivity [18] Chesson, et al., the exposed intensity of muscular activity is directly proportional to postictal elevation of serum CK [19]. It is documented that the magnitude of the rise of postictal serum CK is a more delicate indicator of GTC epileptic seizures as compared to its absolute levels. In another study Neufeld et al. established that a significant rise of CPK levels follows 2<sup>nd</sup> day of GTC seizures, even though the serial tests are within the normal range. They further noted that a rise of at least 15 U/L is extremely suggestive of an event of epilepsy [20]. Various studies proposed a powerful linkage of high serum CPK values with a seizure may be the principle reason for loss of consciousness. Though CPK evaluation has extraordinary specificity it has shown to have only modest sensitivity [19,21].

The foremost emphasis of our research was to evaluate the relationship of WBC count with seizures. While swotting the already available literature, we could not discover any systematic scrutiny of WBC counts about an alone seizure. Total leucocyte count was determined in our study and values of 13639 leucocytes per cubic millimeter of blood was found in the epileptic group, which was quite higher than the normal value so it showed that rise in the TLC might be due to release of hormones like catecholamine's and cortisol in epileptic patients due to stress, responsible for the release of leucocytes from the bone marrow. On the other hand in pseudo seizure mean TLC value was less than the patients of seizures 8283 leucocytes per cubic millimeter of blood and in control subject its mean TLC value was 6851 leucocytes per cubic millimeter of blood. Therefore we concluded that values were not within the normal range in patients having seizures which might be due to the release of hormones from the higher centers. Thus the determination of total leucocyte count might be an adjuvant test to distinguish epileptic seizures from pseudo seizure.

In a study conducted by Shah, et al., it was documented that somewhat more than 75% of generalized seizures are linked with a noteworthy rise in WBC count. It was further noted by them that there was infrequent rise in WBC count in complex partial seizures, however high WBC count was not linked with events like NES or SPS [22].

### CONCLUSION

The present study proves the relationship of inflammation with epilepsy and variations in respective hematologic parameters. Raised WBC levels may be a result of on-going inflammatory progressions in the pathogenesis of epilepsy so it is concluded that serum CPK and TLC may serve as differentiating markers between epileptic generalized tonic-clonic seizures (GTCS) and pseudo seizures.

### DECLARATIONS

#### Conflicts of Interest

The authors declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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