CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
http://doi.org/10.5281/zenodo.3547577

Available online at: http://www.iajps.com Research Article

SIGNIFICANCE OF PROLACTIN & CREATINE PHOSPHOKINASE IN EPILEPSY (GRAND MAL) AND PSEUDO SEIZURES IN FEMALE POPULATION

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Abstract:

Back Ground & Objectives: *One of the important neurological disorders: Epilepsy is marked by sudden recurrent episodes of sensory instabilities, unconsciousness, or convulsions linked with abnormal actions of the brain. Review of literature exposed very partial research studies considering a combination of and serum Prolactin (PRL) and Creatine Phospho kinase (CPK) and as markers for differentiating epileptic and psychogenic non epileptic seizures (PNES). Therefore, in the present study, we analysed the role of serum PRL and CPK, individually and in combination to evaluate the significance of the levels of PRL & CPK in female Patients of Grand Mal epilepsy and Pseudo seizures.*

Methodology: *We conducted this cross-sectional study in a tertiary care medical teaching hospital over a period of 2 years after getting ethical approval from Advance Studies & Research board. We recruited ninety female subjects in our study and divided them in three groups, each of which comprised of 30 subjects. Statistical analyses were done using SPSS 21. ANOVA was used to compare the results of the different groups. P< 0.001was taken as significant*

Results: *The results of this study showed significant difference between the levels of PRL & CPK among three groups. Both PRL & CPK were found higher in epileptic group as compared to pseudo-seizures and control group (p <0.001)*

Conclusion: *The study concluded that both Prolactin & Creatine Phosphokinase may be used as reliable biochemical marker in the diagnosis of grand mal seizures in females and segregating it from pseudo-seizures in female patients.*

Key words: *Creatine Phosphokinase, Prolactin, Generalized Tonic-Clonic Seizures, Pseudo-Seizures*

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Please cite this article in press Farhat Ijaz et al., ***Significance Of Prolactin & Creatine Phosphokinase In Epilepsy (Grand Mal) And Pseudo Seizures In Female Population.,*** *Indo Am. J. P. Sci, 2019; 06(11).*

INTRODUCTION:

Sudden uncontrolled disturbance or unexpected burst of electrical activity in the brain which may cause changes in one's behaviour, movements or feelings & level of consciousness is referred as an episode of Seizure. In other words we can say that Seizure is the clinical manifestations of physical convulsions, abnormality in behaviour & even unconsciousness. Seizures are much common than we actually think. It was found that about 10% of people have at least 1 epileptic seizure in their lives [(1)]It is worth mentioning that Seizure can occur after a closed Head Injury, stroke and brain infection like Meningitis or some other illness. Many times the cause is unknown. It is characterized by excessive, abnormal synchronous neuronal discharges of neurons located principally in cerebral cortex [(2)]

Most seizures disorders can be managed with medications but controlling of seizures can still have a noteworthy influence on ones daily routine & life. Signs & symptoms of the seizures may range from mild to severe & vary depending upon the type of seizure [(3)].

If any one has two or more episodes of seizures or has a tendency to have recurrent seizures, he is said to have developed Epilepsy [(3,4)]. Epilepsy may be represented as:- a) Two episodes of seizure over a period of 24Hours, b) one unprovoked seizure and a possibility of additional seizures in next 10 years similar to the general reappearance risk at least 60% after two unprovoked seizures c)Epilepsy syndrome.[(3)] Chance of experiencing second seizure after an episode of first seizure is about 50% [(1,3)] Studies revealed that Epilepsy affects about 1% of population at any given time & about 4% of the population affected at some point in time. 80% of those with Epilepsy live in developing countries [(4)]

Seizures of many types are documented which range in severity. Their types vary how they begin & from where they originate. Most last from 30sec to two minutes. Longer than 5 minutes seizures is definitely a medical emergency. Depending upon on how & where they originate seizures is generally classified as Focal or Generalized seizures. Generalized seizures may be Absence Seizures or Petit Mal seizures, Tonic seizures, Atonic seizures, Clonic seizures, Myoclonic seizures, Tonic clonic seizures or Grand Mal seizures (GTCS)[(2,5)]

Pseudo seizure or hysterical seizures or psychogenic seizures are well known older terms for the events that appear to be epileptic seizures but in fact do not represent the manifestation of excessive synchronous cortical activity. They are clearly of psychogenic origin and documented as change in behaviour or consciousness. Most standard current terminology is Psychogenic non epileptic seizures (PNES) or Psychogenic non epileptic episodes (PNEE) They are characterized as a expression of dissociative or somatoform (conversion) disorders [(6,7)]

Recording of an epileptic seizure through Video-electroencephalogram (EEG) is considered to be the gold standard for the diagnosis [(3,5)] It is to be noted that under video monitoring not all patients present with seizures. Additionally, it is not necessary that all epileptic seizures yield noticeable fluctuations in the scalp EEG. Previous studies showed the incidence of PNES to be 1.4–4.9/100,000/year while in another study the prevalence between 2 and 33/100,000, making it a noteworthy neuropsychiatric situation. [(5,6,7)]

It is observed that patients are on antiepileptic medications for years by the time these patients are appropriately recognized which not only lead to needless healthcare costs but also a wrong diagnosis. Patient becomes exposed to long-term adverse effects of anticonvulsant drugs. Besides huge expenses of therapy, social implications make it essential for accurate diagnosis, before starting the treatment [(1,3,4)]. Many studies have been done on the separate use of serum Creatine phosphokinase (CPK) and Prolactin (PRL) to differentiate epileptic seizures from PNES. Initial studies presented hopeful results yet they were critiqued for several weaknesses in the design of the study. It is worth mentioning that if these tests are freely accessible in all locations and cost-effective, these are the best tools to differentiate Epileptic seizures from Pseudo seizures

Literature review exposed very inadequate studies allowing grouping of PRL and serum CPK as indicators for segregating epileptic and non epileptic seizures. Hence in our study we investigated the role of serum PRL and serum CPK, exclusively and in combination to differentiate epileptic and PNES.

METHODOLOGY:

We conducted our study in a tertiary care medical teaching hospital of Lahore over a period of 2 years after taking approval from Advance Studies & 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 in three groups, each of which comprised of 30 subjects:

Group-1: Patient with confirmed previous history of grand mal seizures and including freshly diagnosed cases of GTCS. (n=30)

Group-2: Patient with history of pseudo seizures. (n=30)

Group-3: Control group: Females of comparable age (n=30).

Young female of child bearing age of 16 to 35 years, having history of seizures were included in our study. Patients with history of Head Trauma, Brain tumour, Meningitis, Cerebro vascular accidents, metabolic disorders (Hypoglycaemia, hypocalcaemia), Muscle injuries and mental impairment were excluded. Pregnant and lactating females were also excluded from the study

Blood sample of 5ml within 30 minutes of a seizure or pseudo seizure was collected. The samples were sent to centre of nuclear medicine (CENUM) of Mayo Hospital, and pathology department of King Edward Medical University Lahore for processing within 24 hours. Serum prolactin (PRL) was determined by radio immuno assay (RIA) using an automated Gamma Counter machine (Model-Genesys TM 5000 Series LTI U.S.A) while serum creatine phosphokinase (CPK) was measured by randox kit using Biochemical Analyser (Model AE-600N). Statistical analyses were performed using Statistical Package for the Social Sciences for Windows 16.0 (SPSS Inc., Chicago, IL, USA). Results were presented as the Mean ± Standard Deviation (SD). Statistical analyses were done using SPSS 21ANOVA was used to compare the results of the different groups. Statistical significance was set at P< 0.001.

RESULTS:

The mean age of female included in control, pseudo-seizure and epileptic group was 23.4± 4.7 year, 21.9 ± 5.5 year and 21.6 ± 4.1 year respectively. The age limit in all female was 16 to 35 years. The mean age in both 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 & 0.098 respectively)

Mean serum Prolactin in pseudo-seizures groups was 8.2±4.8 ng/100ml, in epileptic group was 44.5±5.3 ng/100ml and in control group the mean prolactin was 4.6±3.2 ng/100ml. On applying analysis of variance (ANOVA) we found significant difference between the levels of prolactin among three groups. Further statistical analysis showed that prolactin was significantly higher in epileptic group as compared to pseudo-seizures groups and control (p-value < 0.001) and prolactin was also higher in pseudo-seizures when compared to control group (p-value < 0.001)

Mean serum CPK in pseudo-seizure groups was 130.1 ± 74.3 IU/100ml, in epileptic group was 257.7 ± 24.6 IU/100ml and in control group the mean CPK was 79.9 ± 27.7 IU/100ml. On applying ANOVA we found significant difference between the levels of CPK among three groups, on further investigations we found that serum CPK was higher in epileptic group as compared to pseudo-seizures groups and control (p-value < 0.001) and CPK was also higher in pseudo-seizures when compared to control group (p-value < 0.001). This is shown in Table 3 and graphically depicted

An overall comparison of all biochemical parameters in three groups is shown in Table 1.

Table 1: Overall comparison of biochemical parameters in different groups

Variable	**Control (n = 40)**	**Pseudoseizure (n = 30)**	**Epileptic (n = 30)**	**p-value**
Age (year)	23.4±4.7 (range: 18-32 y)	21.9 ± 5.5 (range: 16-31 y)	21.6±4.1 (range: 16-32 y)	0.38
Serum Prolactin (ng/100ml)	4.6±3.2	8.2±4.8	44.5±5.3	0.0001
Serum CPK (IU/100ml)	79.9±27.7	130.1±74.3	257.7±24.6	0.0001

DISCUSSION:

According to our results, a significant difference in the PRL levels between true epileptic patient (Grand mal) and those with pseudo seizers was noted. Levels of PRL were significantly higher in epileptic group than the pseudo seizure group and mean PRL level in both groups was higher as compared to the healthy control group. Our results are in matching to the outcome of a latest study conducted by Priyanka et al [8] in which PRL was 37 ng/ml in patients of generalized clonic seizures. On the contrary the level of PRL was 16.8ng/ml in the patients of psychogenic non-epileptic seizures and 16.5ng/ml in control group. It was noted by Bauer et al [9] that in about 60% of complex partial seizures there was rise of PRL levels which is due to intensity of epileptic discharges. Postictal PRL levels can be used to discriminate epileptic from psychogenic seizures as there was no rise of PRL hormone detected after psychogenic seizures. Bauer further observed that PRL secretion may decline in repetitive seizures like in cases of status epilepticus probably due to reduced spread of ictal discharge[9]. Malkowicz et al [10] determined the PRL levels after 24 hours seizures which were monitored by video EEG intracranial monitoring. It was seen there was a significant postictal PRL elevations in those patients having longer seizures free intervals while the PRL responses were reduced in subjects having shorter seizures free intervals suggesting that amount of PRL hormone released from the hypothalamus is depleted by seizures or by PRL inhibit feedback mechanism [10]. In a study conducted, in children it was observed that mean PRL level was 28.6 ng/ml in epileptic while in pseudo-seizure and in control groups PRL was 10.4ng/ml and 9.8 ng/ml respectively. It was proposed that abnormal electrical discharge in epileptic seizures passes through the hypothalamic nuclei responsible for elevation of PRL Singh et al and Ahmad et al [11,12] stated parallel results viewing that generalized epileptic seizure cause noticeable early increase of PRL with more increase following prolonged seizures in children [11,12]. Our study results about PRL are further supported by the findings of Pritchand at al , Tharyan et al , Pohlmann et al and Mahmud at al they also reported higher serum PRL in epileptic patient.[13,14,15]

Thus it may be concluded from these studies that serum PRL is a valuable biochemical indicator to differentiate between epileptic and pseudo-epileptic seizures. However, there are some limitations in this regard. Fisher et al [16] has recently described that a lot of previous trials have studied the relationship of serum PRL levels with epileptic events but use of serum PRL levels in clinical practice to diagnose epilepsy or to discriminate epileptic seizures from psychogenic seizures is still controversial because of some limitations which have been described by authors of different studies. One of these limitations includes intrapersonal and interpersonal variations in the basal serum PRL levels, so it is difficult to label significant PRL rise in different individuals. In a study by Aydin et al [17], blood samples were taken at intervals of 5 minutes, 1 hour, 24 hours and 48 hours following epileptic or non-epileptic seizures. Result showed that serum PRL level was highest at 5 minutes intervals following an epileptic seizure and then gradually declined at 1 hour, 24 hour and 48 hour intervals respectively. Second limitation is sensitivity of serum PRL level. Willert et al [18] had revealed that the sensitivity of serum PRL level is greater as compared to neuron-specific enolase (NSE) and creatine phospho kinase (CPK) but specificity of it is less in differentiating epileptic seizures from the psychogenic non-epileptic seizures due to large intra- and inter individual serum level differences. This is also confirmed by results of a study conducted by Tumani et al [19].Thus there is a high probability of getting false positive values by using serum PRL levels alone for this purpose. Thus limited discriminatory power of PRL measurement makes it questionable value in differentiating between epileptic and pseudo-epileptic seizures Alving [20]. A third limitation is that serum PRL assessment does not distinguish epileptic seizures from syncope as described in a review by David et al (2005). In practical setting, most of the seizures occurred at home or non-hospital settings where it is not feasible to measure serum postictal PRL levels, while in hospitals settings video EEG monitoring facility is present which is considered a better tool for this purpose (Fisher et al 2016) [21]. Moreover, there are many factors, which influence the release of PRL from hypothalamus. Among these factors, environmental temperature, and nutritional status influence the synthesis as well as the release of other hormones from the hypothalamus. As temperature is very high in our country, it may be a possible factor responsible for the slight decrease in release of PRL hormones in our patients. Further, most of our patients belonged to low social economic group and were protein malnourished that may decrease release of PRL in these patients as compared to European people in which levels of protein were found to be significantly higher due to cold weather and good intake of dietary proteins.

We in this study also determined the levels of serum CPK. The mean CPK level in our patients was 257 U/100 ml in epileptic group which was significantly elevated after epileptic seizure due to severe muscular contraction. But on the other hand the mean CPK level was 127.60 U/100 ml in pseudo-seizure group which was quite low as compared to the epileptic group but this figure is

slightly higher as equated to the control group in which the mean CPK value was 70.77 U/100 ml. Thus, CPK was higher in epileptic group as compare to the pseudo-seizure groups as well as 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 in Iran (2009), mean CPK concentrations were significantly higher in patients of GTCS, in which serum CPK concentrations had a sensitivity of 75% and specificity of 86% for the diagnosis of GTCS. In that study, the levels of CPK was found above 160 ml/dl in 75% of the patients of GTCS.

In summary, according to our results there was significant rise in serum CPK & PRL levels after true epileptic attack (Grand mal) that may serve as differentiating marker than that of pseudo seizers.

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