



## A STUDY ON ROLE OF PROLACTIN AND CREATINE PHOSPHOKINASE IN THE DIAGNOSIS OF NEW ONSET SEIZURES

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### KEYWORDS :

#### INTRODUCTION

A seizure is a transient occurrence of signs or symptoms due to abnormal, excessive, or synchronous neuronal activity in brain.

The meaning of the term seizure has to be carefully differentiated from that of epilepsy. Epilepsy can be described as a condition in which a person has recurrent seizures episodes due to a chronic, underlying process. Epilepsy can be referred to as a clinical phenomenon rather than a single disease entity as there are many different forms and causes of epilepsy.

It was estimated that 1.5% to 5.0% of persons in any kind of population would have a seizure at some time. Focal aware seizures, with or without secondary generalization, are the most common seizure type, followed by GTCS. Other seizure types, such as absence, atonic, or myo-clonic, are relatively uncommon.

Psychogenic non-epileptic seizures (PNES) is accounting for a majority of non-epileptic paroxysmal events. These are emotionally triggered episodic, and non-epileptic events, or spells that can be difficult to distinguish from epileptic seizures, even for a trained observer. They occur in patients with and without epilepsy and vary in their etiologies. Some are because of somatoform disorders, or malingering, or factitious disorder.

Two observational tools are clinically useful to make the diagnosis. One is the avoidance of testing maneuvers, such as releasing the hand of the patient over the face. This may terminate seizure due to resistance in case of a psychogenic seizure, though some patients may allow their hand to strike the face. Another observational tool in inducing the psychogenic seizures by methods such as hyperventilation, saline infusions.

Seizures can easily be confused with other diagnoses like syncope, transient ischemic attack, or migraine, but they are mostly confused with non-epileptic seizures of psychogenic origin.

A positive EEG is the gold standard investigation to establish the diagnosis of epilepsy and, in a few cases, to evaluate seizure type and syndrome. In contrast, a negative EEG result does not rule out the diagnosis of epilepsy. The most reliable method is video-EEG registration of all the investigative methodologies available.

Unfortunately, not all epilepsy centers or neurologists have access to video monitoring most of the time.

In India, such modalities like video-EEG are not easily available, and hence cheaper, and easily accessible alternative investigations are required.

An incorrect diagnosis exposes the patient to long-terms

adverse effects of anti-epileptic drugs, the unnecessary expense of therapy, and above all, social implications, which make it essential to diagnose seizures accurately before starting the treatment of seizures.

One study showed that the coexistence of pseudo-seizures with epilepsy is as high as 33%.'

It would be beneficial to identify another surrogate measure of epilepsy for an accurate diagnosis.

Elevation of Prolactin in serum following seizure has been considered as a potential candidate for a surrogate marker.

The first study was done to evaluate the correlation between an elevation of Prolactin in serum and epilepsy was published in 1978 by Trimble, who showed that a GTCS increased prolactin serum level, but psychogenic non-epileptic seizures did not.'

In another smaller but more rigorous trial (using video EEG recordings), the authors did not find serum CPK levels to be useful in differentiating seizures from other causes of loss of consciousness.

In one retrospective study, total CPK measured at least three hours after the event correlated with generalized seizures.

#### Aim Of The Study:

To evaluate the role of Prolactin and total CPK levels in relation to Status-epilepticus

Types of seizure, time interval after seizure, duration of seizure episode. To differentiate tire seizures from non-epileptic seizures.

A seizure is a transient occurrence of signs or symptoms due to abnormal, excessive, or synchronous neuronal activity in the brain.

#### MATERIALS AND METHODS

##### Hospital based study

Design — It is a Prospective observational study were done in R L JALAPPA HOSPITAL. fifty one patients with a probable diagnosis of new-onset seizures were included in the study. Serum prolactin level was measured in the chemiluminescence method, CPK levels were measured by CK-NAC (creatin kinase-N acetylcysteine) method during the study. Other investigations like renal function test, CBC, RBS, serum electrolytes, serum calcium, and magnesium were also done. Cerebral imaging and EEG were also done.

Normal prolactin levels: male: 2-18 rig/ml

non pregnant female: 2-29ng/dl

pregnant female: 10-209ng/dl

Normal creatine phosphokinase levels: male: 46-171 units/l

Female: 24-145units/l

**Inclusion criteria**

- Patients suspected to have new-onset seizures who presented within 5 hours of onset.

**Exclusion criteria**

- Known epileptics who were on or off treatment.
- Pregnant women.
- Patients with known endocrine disorders.
- Patients with renal disorders.
- Patients who have taken any intramuscular injections just before coming to the hospital.
- Patients who have presented after 5 hours of seizures

On admission, a careful and detailed history was recorded, and a thorough clinical examination was conducted. All the points which were mentioned in the proforma in the annexure-I were recorded. Additional information, if any, was recorded, and routine investigations like CBC, renal function test, RBS, electrolytes, serum calcium, and magnesium were carried out. Total CPK and serum prolactin were also ordered on admission. Patients were also advised to undergo cerebral imaging and EEG.

**RESULTS**

Distribution of patients according to type of seizure

Type of seizure	No. of Patients (n =51)	Percentage Of Patients (%)
GTCS	21	40
Focal onset Seizure	14	28
Complex Partial Seizure (focal impaired awareness seizures)	9	18
Status Epilepticus	4	8
PNES	3	6

Type of seizure	No. of Patients (n =51)	Prolactin}	0-1 Hour Prolactin}	1-3 Hour Prolactin }	>3 Hour Prolactin }
GTCS	21	12	5/12 (50%)	7/19 (41.66%)	1/12 (8.33%)
Focal onset Seizure	14	5	2 /5 (40%)	3 /5(60%)	0/5 (0%)
Complex Partial Seizure (impaired awareness seizures)	9	2	1/2(50%)	1/2 (50%)	0/2 (0%)
Status Epilepticus	4	4	2/4 (50%)	2/4 (50%)	0/4 (0%)
PNES	3	0	0 (0%)	0 (0%)	0/ (0%)

Distribution of Patients According To EEG Characteristics

EEG	No. of Patients (n =51)	Percentage Of Patients (%)
Normal	31	61
Abnormal	20	39

**Distribution of Prolactin According to Type and Presentation after Seizures**

GTCS and CPS (focal impaired awareness seizures) group of patients were predominantly brought to us with more than one seizure, whereas focal seizure patients presented with a solitary episode. Four patients presented with status

epilepticus, and three patients were of probable PNES presented to the hospital with multiple episodes.

93.75% of patients with GTCS who presented within three hours had elevated CPK, whereas 90.9% of patients with FS had elevated CPK within three hours.

The majority of patients with GTCS had both Prolactin and CPK markers elevated. All patients of SE had both the markers elevated. All patients with PNES had normal markers levels.

Distribution of CPK According To Type and presentation after Seizures

Type of seizures	No. Of patients (n=51)	TOTAL CPK increased	0-1 HOUR CPK increased	1-3 HOUR CPK increased	3 HOURS CPK increased
GTCS	20	16	6/16 (37.5%)	9/16 (56.25%)	1/16(6.25%)
Focal onset Seizure	14	11	5 /11 (45.45%)	5/11(45.45%)	1/11 (9.09%)
Complex Partial Seizure (impaired awareness seizures)	9	3	1/3 (33.33%)	2/3 (66.66%)	0/3 (0%)
Status Epilepticus	4	4	1/4 (25%)	2/4 (50%)	1/4 (25%)
PNES	3	0	0 (0%)	0 (0%)	0 (0%)

**DISCUSSION**

The study was conducted on 51 patients of probable new-onset seizures admitted in the intensive care unit and various wards of the General Medicine department

**Serum Prolactin in GTCS**

- Our study confirms the previous observation that serum prolactin increases following generalized onset tonic-clonic seizures.
- The majority of patients 9/10 (90%) of GTCS who presented within the first hour after seizure led raised prolactin levels.
- Only 30% of GTCS patients who presented between 1-3 hours after seizure had raised PRL, whereas only 12% of patients presented after 5 hours of seizures had elevated PRL.
- Our findings were comparable to the results of various study groups, who concluded that if serum prolactin level was measured 10 to 20 minutes after an event, it could probably be a useful measure to differentiate between a generalized tonic-clonic seizure and psychogenic non-epileptic seizures.
- However, if a serum prolactin test is done 5 hours after the event, it probably indicates the patient's baseline prolactin level.
- In one study, Willet et al. observed 32 patients with postictal epileptic seizures, with a rise in serum prolactin levels up to 6 hours when compared with baseline prolactin level.
- Meierkord et al. reported that the duration of seizure has no significant effect on prolactin levels, which was concordant to our findings of the study and other study group
- The elevation of prolactin levels was also correlated to the number of episodes of GTCS with which patients presented to us. It was observed that the more episodes of GTCS, there were more chances of patients having raised prolactin levels.

**Serum Prolactin in focal onset seizures**

- 70% of patients of focal onset seizure who presented within one hour after the event had elevated prolactin levels.
- Only 20% of patients of focal onset seizures presented between 1-3 hours after seizures had raised PRL levels.
- It was observed that patients who had focal onset seizures with secondary generalization had more chances of presenting with raised PRL levels.
- In one study, it was seen that in focal onset seizures, decreased occurrence of prolactin rise was due to the decreased spatial involvement and intensity<sup>5</sup>.

#### Serum Prolactin in CPS (focal impaired awareness seizures)

- Our study observed that only 22% of patients who were presented to us with CPS (focal impaired awareness seizures) had raised PRL.
- Our observation findings could not correlate with the number of seizure episodes and time of presentation to us after the seizure episode. However, the number of patients of CPS (focal impaired awareness seizures) in our study was small.
- In various studies, it was observed that mean prolactin levels were significantly elevated only in GTCS and CPS (focal impaired awareness seizures) than focal seizures<sup>47</sup>
- It suggests the possibility of a correlation between the degree of prolactin elevation and the extent of activity of epilepsy.
- In GTCS, there is a presumed spread of electrical activity from the ventromedial hypothalamus, leading to the release of prolactin regulator into the hypophyseal portal system. This could either be a direct stimulator of prolactin release or an inhibitor of prolactin-inhibiting factor
- Nor-adrenaline, Dopamine, gamma-aminobutyric acid (GABA) are considered inhibitors to prolactin secretion.
- Most CPS (focal impaired awareness seizures) originate in the temporal lobe of the brain. It was demonstrated that the electrical activity spreads from the medial temporal structures to the limbic system, even before the actual ictal manifestations are observed
- Cases, which were not exhibiting a rise in PRL, probably originated in the frontal lobe and supplementary motor cortex with no limbic system involvement.
- Other reports are suggesting that prolactin levels are elevated in temporal lobe CPS (focal impaired awareness seizures) and not in frontal lobe structures CPS.
- Sperhng observed that only high frequency (+10 Hz), unilateral or bilateral discharges from the limbic system, lasting for more than 20 seconds, spread to subconical areas. These might have triggered the ventromedial hypothalamus.
- Discharges of lower or variable frequency, of shorter span or did not involve the limbic regions, did not propagate to these areas.
- It was suggested that when ictal discharges spread from the medial temporal lobe structures to the hypothalamic nuclei, they also close consciousness.
- This may explain the reason for more cases of GTCS and CPS (focal impaired awareness seizures) had raised levels of prolactin.

#### Serum Prolactin in PNES & differentiating it from true seizures

- All patients who presented to the hospital with probable PNES (pseudo-seizures) led normal Prolactin levels.
- It was observed that there was no correlation between time of presentation and number of episodes of seizures of patients with PNES.
- Our study indicated that there was no correlation between levels of serum PRL and the presence of exaggerated motor activity, which had also been observed in another study.
- Estimation of serum prolactin level was considered as one of the methods to be used to differentiate true seizure from

PNES.

- Many studies addressing this issue have concluded that serum PRL levels are significantly elevated after a true seizure but not after PNES.
- Singh and Jana found the mean prolactin level in 15 patients with generalized seizures was 28.6 rig/ml versus 10.4 rig/ml in 8 patients with PNES (P 0:001).
- Similar results were obtained in a larger study done by Kurlemann et al. in which the authors observed that a two- to threefold increase in PRL levels in patients after either GTCS or CPS, but not after the psychogenic seizures.
- Some studies have detected that much higher elevations of PRL levels in GTCS, compared with either partial seizures or PNES.

#### Serum Prolactin in status epilepticus (SE)

- Four patients presented to the hospital with SE. All the patients in this group had elevated Prolactin. They led a two to threefold rise in prolactin levels.
- In repetitive epileptic seizures, the seizure-free interval between the seizures may be essential to determine the serum prolactin levels.
- In one study serum prolactin level was within the normal limits in all CPS cases (focal impaired awareness seizures) and GTCS.
- All patients, who represent three different types of status epilepticus, had prolactin levels within the normal limits, and there was no elevation from baseline values.
- It was postulated that it is due to the different nature of the epileptic discharges or that there may not be a spread of paroxysmal activity to hypothalamic neurons in the absence of seizures.
- In contradiction to other studies, all the patients who presented with status epilepticus had elevated Prolactin in our study.

#### CONCLUSION

- We conducted a study on 51 cases of new-onset seizures.
- 40% of patients presented to us with GTCS, of which 90% of patients who presented within one hour had raised PRL, and 90% of patients had raised TLC, and 91.66 % of patients had elevated total CPK levels.
- 28% of patients presented to us with focal onset seizures, of which 70% of patients who presented within one hour had raised Prolactin, and 86% & 60% of patients led leukocytosis and elevated total CPK levels, respectively.
- 18% of patients presented to us with CPS (focal impaired awareness seizures), of which only 10% of patients who presented within one hour had raised prolactin & TLC levels, whereas 30% of patients had raised CPK levels.
- All patients presented to us with status epilepticus irrespective of the time of presentation led elevated all biomarkers. i.e., Prolactin, total CPU levels, and TLC levels.
- All patients presented with psychogenic seizures (PNES), irrespective of the time of presentation, they had normal Prolactin, total CPK levels, & TLC levels

#### Summary

- The majority of patients presented with GTCS (90%) presented within one hour had elevated markers.
- 70% of patients who presented to us with focal onset seizures within one hour had raised Prolactin levels, 86% & 60% of patients had leukocytosis and raised total CPK levels, respectively.
- Only 10% of patients who presented to us with CPS (focal impaired awareness Seizures) had elevated Prolactin, and 30% of patients had elevated CPK levels.
- All patients who presented to us with status epilepticus irrespective of the presentation time had elevated prolactin levels, total CPK levels, & TLC levels.
- All patients presented to us with psychogenic seizures

(PNES) irrespective of the presentation time had prolactin levels, total CPK levels, & TLC levels within normal limits.

- When measured in an appropriate clinical setting, a raised serum prolactin assay is a useful additional tool to differentiate true seizures from psychogenic non-epileptic seizures (PNES).
- The best result can be obtained if the tests are done for these markers used within the first hour of the episode of seizure.
- The duration of seizure & time interval after the occurrence of seizure are useful factors to determine PRL & total CPK.
- Levels of Prolactin and CPK are consistently elevated in status epilepticus.

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