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Serum prolactin levels in patients with seizure disorder

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Abstract
Aim: To evaluate whether prolactin levels can be used as a biochemical marker for differentiating between epileptic and non- epileptic seizures, and to correlate the levels with post-ictal duration.
Materials and Methods: This prospective observational study was conducted at the Chattarpati Shivaji Subharti Hospital, Meerut in the Department of Medicine among 50 cases with previously or newly diagnosed seizure disorders presenting to the hospital were selected on the basis of a detailed clinical history and EEG. The serum prolactin levels were measured, from a sample taken within 30 minutes of the event, in all these patients to look for any correlation with seizure disorder or non-epileptic seizures. In case of an admitted patient having a seizure the serum prolactin levels were measured from a sample drawn within 30minutes of the event, and then another sample drawn 24 hours post-event.
Results: Out of total subjects, majority of subjects had generalized seizures (48%), followed by partial seizures (28%). The proportion of subjects having pseudo-seizures was 24%, The mean±SD of postictal prolactin of subjects having generalized type was 1780.31±624.49 (mIU/L) whereas for the subjects having partial seizures was 592.08±509.11 (mIU/L) and for the subjects having pseudo- seizures was 381.15±172.90 (mIU/L). The inter group comparison showed statistically significant difference in the mean postictal prolactin levels in patients of epileptic seizures and pseudo seizures ($p<0.01$).
Conclusion: The levels of serum Electrolytes (sodium, magnesium, calcium) decrease in various types of seizures except PNES in which electrolytes (sodium, magnesium and calcium) showed no significant change while potassium remains nearly normal in all types of seizures. Prolactin estimation can be a useful biomarker to differentiate Epileptic seizures from PNES.

Keywords: serum prolactin, biochemical, seizure disorder

Introduction
A seizure is a paroxysmal event due to abnormal, excessive, hypersynchronous discharges from an aggregate of central nervous system (CNS) neurons. Seizure is defined as an "involuntary alteration of behaviour with or without loss of consciousness accompanied by an abnormal electrical discharge in the brain." These seizures are episodes that can vary from brief and nearly undetectable to long periods of vigorous shaking. Seizures can be partial and generalized. The difference between the two is of loss of consciousness. In partial cases a focal point of the brain is affected. In generalized seizures the impulses comes out from both sides of the brain at the same time. Partial seizures may generalize; start from one site in the brain and spread to involve the whole brain [1].
There are multiple causes of seizure [2], but new-onset epilepsy is the most common cause of a first seizure. One in six patients who present with a single seizure will have an identifiable potential cause such as pre or perinatal brain injury (4.4 percent), cerebrovascular disease (3.9 percent), head injury (3.2 percent), brain tumor (1.7 percent) or alcohol use (0.3 percent) [3].
Seizures have profound hormonal manifestation, and serum prolactin changes have been used to distinguish generalized tonic-clonic seizures from other causes of brief stereotyped disturbances of cerebral function [4]. Serum prolactin rises rapidly after spontaneously occurring generalized seizure and after electroconvulsive therapy, reaching a peak between fifteen and twenty-five minutes after the seizure and reverting to normal in about two hours [5, 6].
In generalized tonic clonic seizures there is presumed spread of electrical activity from the ventromedial hypothalamus, leading to release of a specific prolactin regulator into the hypophyseal portal system [7, 8]. This could either by a direct stimulator of prolactin release or an inhibitor of prolactin-inhibiting factor. The increase in prolactin level is due to abnormal electrical activity within areas of the central nervous system that regulate anterior pituitary hormone release.
In complex partial seizures, the elevated levels of prolactin are seen immediately. Those cases of complex partial seizure not exhibiting a rise in prolactin probably originate in the frontal and supplementary motor cortex without involving the limbic system [9].
In India, video-EEG is not easily available, and hence a cheaper and easily accessible alternative is required. Serum Prolactin levels might be used for differentiating between epileptic, non epileptic and other seizure-like

episodes [10]. In this study, we evaluated whether prolactin levels can be used as a biochemical marker for differentiating between epileptic and non- epileptic seizures, and to correlate the levels with post-ictal duration.

Materials and Methods

The study was conducted at the Chattarpati Shivaji Subharti Hospital, Meerut in the Department of Medicine. It was a prospective Observational study, where 50 cases with previously or newly diagnosed seizure disorders presenting to the hospital were selected on the basis of a detailed clinical history and EEG. The serum prolactin levels were measured, from a sample taken within 30 minutes of the event, in all these patients to look for any correlation with seizure disorder or non-epileptic seizures. In case of an admitted patient having a seizure the serum prolactin levels were measured from a sample drawn within 30minutes of the event, and then another sample drawn 24 hours post-event. All patients with history of seizure, as documented by Oral questionnaire/Clinical History and EEG were included in the study. Patients less than16 years of age and more than 70 years of age, with pituitary or hypothalamic disease, history of cranial surgery or irradiation and patients on drugs known to alter prolactin levels (eg- metoclopramide, phenothiazine antipsychotics, selective serotonin reuptake inhibitors, risperidone, estrogens, oral contraceptives, verapamil, methyldopa, long term PPIs, reserpine, cyproterone acetate, aldosterone antagonists, morphine, cimetidine, metiamide), pregnant, lactating mothers and CKD

Diagnosis: A positive EEG is the gold standard for establishing the diagnosis of epilepsy and for evaluating seizure type and syndrome. Venous blood sample was drawn from anticubital vein of each subject by using aseptic precautions and subjected for following estimations. Serum was analyzed for quantitative estimation of Prolactin by ELISA Method, Sodium and Potassium by Flame photometry, Calcium by OCPC End point Colorimetric Method, Magnesium by Colorimetric Titan Yellow Method.
Baseline serum prolactin levels and serum prolactin levels 15 minutes after the attack of seizure were recorded.
Data was collected and subjected to statistical analysis.

Statistical analysis: Data so collected was tabulated in an excel sheet, under the guidance of statistician. The means and standard deviations of the measurements per group were used for statistical analysis (SPSS 22.00 for windows; SPSS inc, Chicago, USA). For each assessment point, data were statistically analyzed using one way ANOVA. Difference between two groups was determined using student t-test and the level of significance was set at $p < 0.05$.

Results: The proportion of female subjects (78%) was higher than male subjects (22%). Out of total subjects, majority of subjects had generalized seizures (48%), followed by partial seizures (28%). The proportion of subjects having pseudo-seizures was 24%. The mean±SD age of subjects having pseudo-seizures (PNES) was 36.81±8.13 years whereas the mean±SD age of subjects having seizures was 34.72±10.09 years. On comparison of mean age of the two sets of subjects, the difference was found to be statistically non-significant (p=0.48).

Table 1: Gender, type of seizure and mean age among the study subjects

Gender	**N=50**	**%**
Male	11	22
Female	39	78
Type of seizures		
Pseudoseizures (PNES)	12	24
Seizure	38	76
Generalized	24	48
Partial	14	28
	Age (in years)	
	Mean	SD
Pseudoseizures (PNES)	36.81	8.13
Seizure	34.72	10.09
t test	1.07	
p value	0.48	

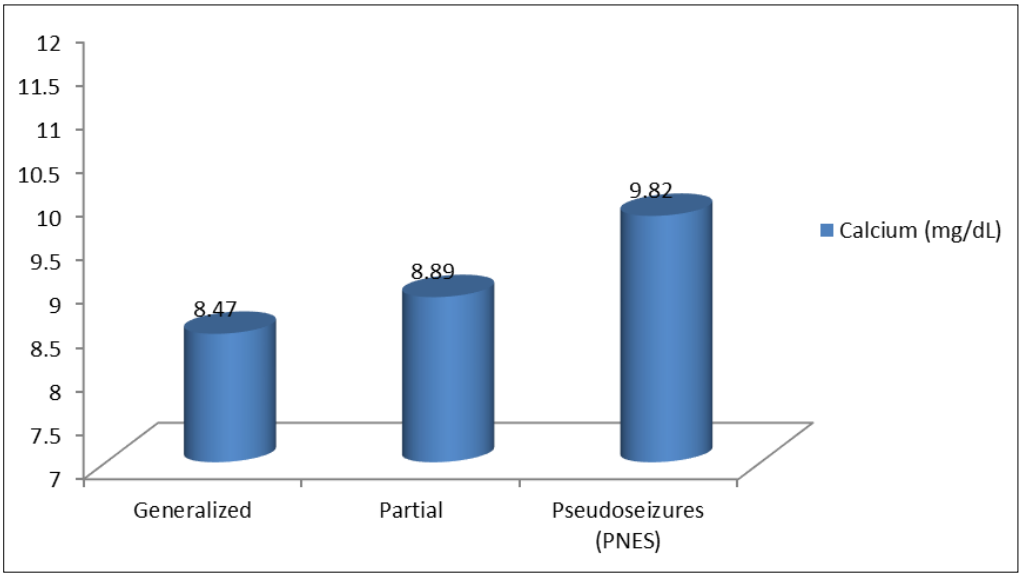
The mean±SD of serum sodium of subjects having generalized type was 131.48±4.93 (mmol/L) whereas for the subjects having partial seizures was 134.79±5.03 (mmol/L) and for the subjects having pseudo- seizures was 137.09±4.56 (mmol/L). The inter group comparison showed statistically significant difference in the mean serum sodium level in various types of seizures (p=0.032). The inter group comparison showed statistically non-significant difference in the mean serum potassium level in various types of seizures (p=0.35) as shown in table 2.

Table 2: Comparison of serum sodium and potassium in various types of seizures

Type of seizures	Sodium (mmol/L)	
	Mean	SD
Generalized	131.48	4.93
Partial	134.79	5.03
Pseudoseizures (PNES)	137.09	4.56
Anova test	4.06	
p value	0.032*	
	Potassium (mmol/L)	
	Mean	SD
Generalized	4.27	0.74
Partial	4.45	0.47
Pseudoseizures (PNES)	4.42	0.50
Anova test	1.02	
p value	0.35	

*: statistically significant

The mean±SD of serum calcium of subjects having generalized type was 8.47±0.68 (mg/dL) whereas for the subjects having partial seizures was 8.89±0.78 (mg/dL) and for the subjects having pseudo- seizures was 9.82±0.99 (mg/dL). The inter group comparison showed statistically significant difference in the mean serum calcium level in various types of seizures (p=0.022) as shown in graph 1.



Graph 1: Comparison of serum calcium (mg/dL) in various types of seizures

The mean±SD of serum magnesium of subjects having generalized type was 1.43±0.16 (mg/dL) whereas for the subjects having partial seizures was 1.68±0.26 (mg/dL) and for the subjects having pseudo- seizures was 1.85±0.14 (mg/dL). The inter group comparison showed statistically significant difference in the mean serum magnesium level in various types of seizures (p=0.031) as shown in table 3.

Table 3: Comparison of serum magnesium (mg/dL) in various types of seizures

Type of seizures	Magnesium (mg/dL)	
	Mean	SD
Generalized	1.43	0.16
Partial	1.68	0.26
Pseudoseizures (PNES)	1.85	0.14
Anova test	4.32	
p value	0.031*	

*: statistically significant

The mean±SD of baseline prolactin of subjects having generalized type was 341.44±70.97 (mIU/L) whereas for the subjects having partial seizures was 329.56±74.52 (mIU/L) and for the subjects having pseudo- seizures was 313.82±64.71 (mIU/L). The inter group comparison showed statistically non-significant difference in the mean baseline prolactin levels in patients of epileptic seizures and pseudo seizures (p=0.42). The mean±SD of postictal

prolactin of subjects having generalized type was 1780.31±624.49 (mIU/L) whereas for the subjects having partial seizures was 592.08±509.11 (mIU/L) and for the subjects having pseudo- seizures was 381.15±172.90 (mIU/L). The inter group comparison showed statistically significant difference in the mean postictal prolactin levels in patients of epileptic seizures and pseudo seizures ($p<0.01$) as shown in table 4.

Table 4: Comparison of mean baseline prolactin levels in patients of epileptic seizures and pseudo seizures

Type of seizures	Baseline Prolactin (mIU/L)	
	Mean	SD
Generalized	341.44	70.97
Partial	329.56	74.52
Pseudoseizures (PNES)	313.82	64.71
Anova test	2.64	
p value	0.42	
	Postictal Prolactin (mIU/L)	
	Mean	SD
Generalized	1780.31	624.49
Partial	592.08	509.11
Pseudoseizures (PNES)	381.15	172.90
Anova test	14.96	
p value	<0.01*	

*: statistically significant

Discussion: Differentiating between pseudo-seizure presenting in an epileptiform manner and epilepsy presents major diagnostic difficulties. Distinction between the two conditions is very important, however, since management of the two disorders differs a lot. This problem of misdiagnosis can be solved by measurement of serum prolactin level electrolyte panel in the postictal phase of epileptic patients in to differentiate between Generalized and Partial seizures.

The proportion of males and females were found to be 22% and 78% of the subjects. Hence there was dominancy of females in the current study. Awasthi P *et al* [11] in their study also found higher percentage of males as compared to females. The finding is in contrast to the fact provided by McHugh JC *et al* [12] in his review where agreement between studies have been reported that females have a marginally lower incidence of epilepsy and unprovoked seizures than males. This difference is usually attributed to male's greater exposure to risk factors for lesional epilepsy and acute symptomatic seizures.

The current study reported that the majority of subjects had generalized seizures followed by partial seizures and subjects having pseudo-seizures were least. The same pattern of subjects enrolled in the study were observed by Alving J [13]. A study done by Parihar P *et al* [1]. have reported that Partial seizures, with or without secondary generalization, are the most common seizure type, followed by generalized tonic-clonic seizures.

The current study reported that the mean age of subjects having pseudo-seizures (PNES) was higher than subjects having seizures. It was in contrast with finding of study conducted by Alving J [13] in which no difference in the mean age was observed among the two sets of patients.

The current study reported that the mean serum sodium of subjects having generalized type was lowest in comparison to the subjects having partial seizures for the subjects having pseudo- seizures. Similar trend was observed in the study conducted by Parihar P *et al* [1]. 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 severe and rapidly evolving hyponatremia include seizures [14].

In the current study the mean serum level potassium was highest for the subjects having partial seizures in comparison to other type of seizures but the difference was statistically non-significant which is in accordance with study conducted by Parihar P *et al* [1]. 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, and seizures do not occur. Changes in the extracellular potassium level (serum levels) have predominant and profound effects on the function of the cardiovascular and neuromuscular systems. Thus, severe potassium abnormality may provoke fatal arrhythmias or muscle paralysis before CNS symptoms appear [14].

The results of current study showed that the mean serum calcium level highest among subjects having pseudo-seizures followed by the subjects having partial seizures and for the subjects having generalized seizures and the difference was statistically significant which is in accordance with study conducted by Parihar P *et al*.[1] Hypocalcemia is defined as a plasma calcium level of <8.5 mg/dl or an ionized calcium concentration <4.0 mg/dl. Seizures may occur without muscular tetany in patients with hypocalcemia. Seizures occur in 20–25% of patients with acute hypocalcemia as a medical emergency, and in 30–70% of patients with symptomatic Hypoparathyroidism [15, 16].

The results of current study showed that mean serum level magnesium highest among subjects having pseudo-seizures followed by the subjects having partial seizures and for the subjects having generalized seizures and the difference was statistically significant which is in accordance with study conducted by Parihar P *et al* [1].

Symptoms do not appear unless Mg2+ decreases to <1.2 mg/dl, and they may not correlate well with serum ionized Mg2+ levels. The primary clinical findings are neuromuscular irritability, CNS hyperexcitability, and cardiac arrhythmias. Seizures, usually generalized tonic–clonic, can occur in neonates and adults in association with severe hypomagnesemia, at levels <1 mEq/L [14].

Acute and/or severe electrolyte imbalances frequently cause seizures, and these seizures may be the sole presenting symptom. Seizures are especially common in patients with sodium disorders, hypocalcaemia, and hypomagnesaemia [17].

The results of current study showed that the mean baseline prolactin levels of subjects having generalized type was higher in comparison for the subjects having partial and pseudo- seizures but the difference was statistically non-significant. Further, the mean postictal prolactin levels subjects having generalized type was more in comparison to subjects having partial seizures and pseudo- seizures and the difference was found to be statistically significant. The results were in accordance to findings reported by Awasthi P *et al* [11]. Findings of our study confirmed that plasma prolactin levels are unchanged following pseudo seizures. This and other studies by Trimble MR *et al* [18] and Abbott RJ *et al* [19]. Therefore, suggest that estimation of plasma prolactin is useful in differentiating between true and pseudo seizures. However the results of current study are contrary to the findings of Alving J *et al* [13]. who found a statistically significant rise in serum prolactin level after an attack of pseudo seizure.

The mechanism, by which true epileptic seizures induce a short-lived elevation of plasma prolactin following seizures, is not known. Stress causes an elevation of plasma prolactin. However, this is unlikely to be the cause following seizures as it has been shown by Abbott RJ *et al* [19]. that, while serum cortical rises following simulated seizures, prolactin is not significantly elevated.

Our study has several limitations which ought to be properly addressed. The major drawback is the cross-sectional study design which, due to its very nature, does not enable the deduction of direct linkage inferences with regard to the relationship between change in electrolyte panel levels and prolactin levels in the postictal phase of epileptic patients leading to differentiate between Generalized and Partial seizures.

Conclusion

Our study indicates highly raised serum Prolactin levels, only in patients with Generalized Tonic-Clonic Seizure & Complex Partial Seizures. The levels of serum Electrolytes (sodium, magnesium, calcium) decrease in various types of seizures except PNES in which electrolytes (sodium, magnesium and calcium) showed no significant change while potassium remains nearly normal in all types of seizures. Prolactin estimation can be a useful biomarker to differentiate Epileptic seizures from PNES. The serum PRL level usually rises following an epileptic seizure while it remains unchanged in PNES. Hyperprolactinemia has been considered a potential candidate for a surrogate marker in seizures. Seizures often represent an important clinical manifestation of electrolyte disturbances. Seizures are more common in patients with hyponatremia, hypocalcemia, and hypomagnesemia. Successful management of seizure patients begins with the establishment of an accurate diagnosis of the underlying electrolyte disturbances. For that reason, complete serum chemistry, including measurements of electrolytes, especially sodium, calcium, and magnesium, should be part of the initial diagnostic workup in adult patients with seizures.

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