ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

*International Journal of Medical Science and Advanced Clinical Research (IJMACR)*

*Available Online at: www.ijmacr.com*

*Volume – 5, Issue – 2, March - April - 2022, Page No. : 253 - 261*

# Evaluation of Serum Prolactin Level in Patients Presenting with Seizure and Seizure-like Events

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**How to citation this article:** Lakra DP, Khande Manisha, Tiwari Tanushree , "Evaluation of Serum Prolactin Level in Patients Presenting with Seizure and Seizure-like Events", IJMACR- March - April - 2022, Vol – 5, Issue - 2, P. No. 253 – 261.



**Type of Publication:** Original Research Article

**Conflicts of Interest:** Nil

## Abstract

**Introduction:** In developing countries, such as India this figure can be as high as 139 per 100 000**.** It is necessary to find an easily available and cheaper diagnostic test to help identify true seizure events and reduce the treatment gap.

**Materials And Methods:** In our study conducted at Dr Bhim Rao Ambedkar Memorial Hospital ,Raipur from January 2020 –May 2021, all patients presenting with abnormal body movements above the age of >=18 years of age were evaluated and 100 patients were included and compared for serum prolactin level and type of seizure, various etiology and clinical entities.

**Results:** According to type of seizure into focal seizure, GTCS and pseudo seizure; we found that no association could be established in cases of focal seizures with no rise of serum prolactin level within 20 mins (p value =0.95) whereas there was a positive association in cases of GTCS where p value is <0.0001 within 20 minutes.On comparing pseudo seizure 25 patients had serum, the p value is <0.0001, which is statistically significant and we infer that there is negative association of pseudo seizure with raise serum prolactin level.

**Conclusion:** In our study we concluded that there was a increase in serum Prolactin level within 20 minutes of seizure in patients presenting with GTCS which returned to baseline after 24 hours of seizure free interval. We could not form an association in focal seizure.

**Keywords:** Epilepsy, Seizures, Pseudo-seizure,Prolactin level, GTCS

## Introduction

Epilepsy is one of the most common neurological diseases in the world that affects people of all ages.[1] It has been estimated that 49 per 100 000 person were

diagnosed with epilepsy each year in high income countries whereas in low- and middle-income countries, such as India this figure can be as high as 139 per 100.[2] Hence it is essential for accurate diagnosis before starting treatment and submitting our patients to sophisticated and expensive investigation such as EEG,CT BRAIN AND MRI BRAIN etc. Studies have shown that elevated serum Prolactin when measured in appropriate clinical setting at 10 to 20 mins after a suspected event is useful adjunct for differentiation of generalised tonic clinic or complex partial seizures from psychogenic non epileptic seizures. Prolactin[PRL] releases from pituitary is controlled by hypothalamus via PRL inhibitory factor,believed to be dopamine[3].

It has been hypothesized that ictal epileptic activity in medial temporal structures may propagate to the hypothalamus regulation of PRL release; the spread of electrical activity from ventromedial hypothalamus and medial temporal structures leads to release of specific prolactin regulator into the hypophyseal portal system and consequently increase in prolactin.[4]

Elevated serum Prolactin when measured in appropriate clinical setting at 10 to 20 mins after a suspected event is useful adjunct for differentiation of generalised tonic clinic or complex partial seizures from psychogenic no epileptic seizures but it is difficult to differentiate from syncope.

Hence in this study we would like to extrapolate this hypothesis in seizures and also other seizure like events which may be due to epilepsy or any other aetiology and find a cheaper easily accessible non invasive method of diagnosing epilepsy..It can be applied in cases of diagnostic uncertainity between true epilepsy and pseudoepileptic events, before submitting our patients to more sophisticated and expensive investigations. This will reduce the economical burden of such patients and help bridge “the treatment gap”. Hence this study was done to identify the role of serum prolactin in differentiating seizure vs pseudoseizure.

**Methods and Materials**

A cross sectional study was conducted at Dr Bhim Rao Ambedkar Memorial Hospital ,Raipur from January 2020 –May 2021 on 100 patients presenting to Department of medicine, Dr. Bhim Rao Ambedkar hospital, Raipur. After taking a written informed consent from all patients for participation in the study were included.

Hence all patients presenting to Dr. BRAMH hospital,Raipur with seizure and seizure like events was considered for the study. After applying the exclusion criteria ,100 patients were evaluated further.

**Inclusion Criteria**: Age above 18 years with seizure and seizure like events. Giving consent for the study.

**Exclusion Criteria:** Physiological: Pregnancy ,Lactation Tumours :Macro adenoma of pituitary,Suprasellar pituitary mass Meningioma , Dysgerminoma , Rathke cyst Pituitary Hyper secretion : acromegaly ,prolactinoma, Drugs :like phenothiazine bromocriptin, antipsychotics, SSRI, MAO I and some tricyclics, prokinetics, opiates, estrogen, anti-androgens, anti-hypertensive, H2 receptor antagonist, cholinomimimetics Misscellanous: Hypothyroidism

On presentation the seizure and seizure like event was classified into focal or GTCS or pseudoseizure on the basis of history and if clinically witnessed A detailed history was taken from each patient regarding their presenting complaint, associated symptoms, alcohol intake, past medical history etc like seizure. A complete neurological evaluation was done for all patients.

A written informed consent was taken from all patients. Patients giving consent for participation in the study were included. Two blood samples were sent for each patient. The first blood sample was taken within the first 20 minutes of seizure for serum prolactin level whereas the second blood sample was taken after 24 hours of seizure free interval for evaluating the baseline serum prolactin level.

A basic set of investigations were done such as complete blood count, Liver Function Test ,Renal Function Test RBS on the day of admission.

All patients underwent NCCT Head and MRI Brain and EEG in subsequent days of admission.

According to the structural etiology found on NCCT head and MRI brain the patients were further classified into- infective/inflammatory (which includes meningitis, cerebral malaria, autoimmune encephalitis, viral encephalitis): metabolic encephalopathy (hypoglycemic encephalopathy, hypoxic encephalopathy, uremic encephalopathy) cerebrovascular accidents, hemorrhage (SAH, SDH, and EDH), seizure disorder, SOL(AV Malformation,cavernoma,brain abscess, meningioma) and pseudo seizure(PNES).

The collected data were tabulated and statistically analyzed using SPSS© for windows™ Vs 17, IBM™ Corp NY and Microsoft excel™ 2007. Kolmogorove-Smirnove analysis was performed for checking linearity of the data. Chi square test/ Fischer's exact test was used to analyze the significance of difference between frequency distribution of the data. Comparison of mean and SD between two groups was done by using students t test and Analysis of variance (ANOVA). P-value <0.05 was considered as statistically significant.

**Results**

Patient's demographic data showed that the most common age group with seizure and seizure like events were in the age group of 41-50 years (23%).Mostly patients belonged to age of < 60 years hence suggestive of seizures and seizures like events were not so common in the elderly population as observed in our study.

We further classified our patients according to history in focal, GTCS and pseudo seizure;

For the first sample sent(within 20 mins) we found out that there were 8 patients presenting with focal seizure of which 4 patients (8.16%) had normal serum prolactin level (<=17ug/L) and 4 patients(7.84%) had elevated level of serum prolactin(>17ug/L), the p value was found to be 0.95,which is statistically insignificant.

Similarly in patients with GTCS, there were 20 patients (40.8%) in normal serum prolactin<=17ug/L and 46 patients (90.19%) were in the elevated level of serum prolactin>17ug/L, the p value was found to be <0.0001 which is statistically significant

The patients of pseudo seizure were also evaluated and we found that 25 such patients (51.02%) had normal serum prolactin<=17ug/L and 1 patient (1.9%)had elevated level of serum prolactin>17ug/L, the p value came out to be p< 0.0001 which is statistically significant.

In the second sample sent after 24 hours of seizure free interval, all patients with focal seizure 8 of them(9.7%) had normal serum prolactin level<=17ug/L and no patients showed rise in the serum prolactin level>17ug/L, the p value was 0.16 ,which is statistically insignificant.

Similarly in patients with GTCS seizure ,49 of them(59.75%) had normal serum prolactin level<=17ug/L and 17 of them (94.44%) had elevated

level of the serum prolactin>17ug/L, the p value came out to be p 0.005 , which is statistically significant and in case of patients of pseudo seizure 25 of them(30.48%)had serum prolactin<=17ug/L and 1 patient(5.55%) had the serum prolactin level>17ug/L, the p value was< 0.02 which is statistically significant.

In our study we categorized patients into 7 groups according to the etiology; infective/inflammatory (which includes meningitis, cerebral malaria, autoimmune encephalitis, viral encephalitis): metabolic encephalopathy (hypoglycemic encephalopathy, hypoxic encephalopathy) cerebrovascular accidents, hemorrhage (SAH, SDH, and EDH), seizure disorder, SOL, and pseudo seizure and compared to serum prolactin level. For the first sample(within 20 minutes), there were total 49 patients of these 7 etiology with normal serum prolactin level<=17ug/l and 51 of these 7 etiology patients with raised serum prolactin level >17ug/l within 20minutes. For the second sample (after 24 hours) 82 patients had level within normal limit of serum prolactin level.

Out of 15 patients in the group of infective/inflammatory there are 3 patients (6%) in prolactin normal level (<17ug/l) and 12 (23.52%) in serum prolactin level>=17ug/l within 20 minutes. The p value is 0.015, which is statistically significant So we observed that in patients with infective etiology there was association with serum prolactin level within 20 minutes and even after 24 hours , this may be due to the seizures or etiology itself.

Out of 15 patients in the group of encephalopathy there are 9 patients (18%) in prolactin normal level (<17) and 6 patients(40%) in serum prolactin level>=17 within 20 minutes. The p value is 0.35, which is statistically insignificant.. Hence association was present within the first 20 minutes only.

Out of 12 patients in the group of CVA there are 5 patients(10%) in prolactin normal level (<17) and 6 patients(11%) in serum prolactin level>=17 within 20 minutes. The p value is 0.58, which is statistically insignificant. After 24 hours, in the 2nd sample of patients with CVA there were no patient with raised serum prolactin level.

Out of 20 patients in the group of seizure disorder there are 3(6%) in prolactin normal level (<17) and 17 (33.3%) in serum prolactin level>=17 within 20 minutes. The p value is 0.0006, which is statistically significant. No association was found after 24 hours of seizure free interval with serum prolactin level. Hence the rise in prolactin is seen transiently.

In our study out of 27 patients with PNES Out of 27 patients in the group of PNES there are 25 (51.02%) in prolactin normal level (<17) and 2(3%) in serum prolactin level>=17 within 20 minutes. The p value is <0.0001, which is statistically significant.

Similar studies were done which corroborated with our result comparing seizure disorder and PNES.

**Discussion**

We classified our patients according to history in focal, GTCS and pseudo seizure; in these subgroups we found that no association could be established in cases of focal seizures with rise of prolactin within 20 minutes. Positive association was found between GTCS that suggests a rise in serum prolactin within 20 minutes where p value is <0.0001 within 20 minutes.

The p value is <0.0001 for patients of pseudoseizure, which is statistically significant and we infer that there is negative association of pseudo seizure with raise serum prolactin level as majority of these patients have serum

prolactin within normal limit.Similar results were found in other studies such as **Bauer J 1996** stated "Prolactin usually fails to rise after psychogenic seizures, therefore, postictal prolactin levels can be used to differentiate between epileptic and psychogenic seizures." **[5] Shah AK, et al** found that "Serum prolactin level increases above twice the level at baseline after a complex partial seizure or a generalized seizure. We conclude that complex partial or generalized seizures are associated with an increase in serum prolactin level"**[6] Bauer J, et al** held measurement of postictal serum-prolactin concentrations in epileptic seizures in order to distinguish them from psychogenic seizures. A significant rise was seen in 88% of Grand mal seizures, 78% of complex-partial seizures, 22% of simple-partial seizures and 6% of generalized seizures. The discussion of both these general findings is based on the presentation of neuroanatomical and neurophysiological principles of prolactin secretion**.[7] Pritchard PB, et al** conducted study in 6 patients with epilepsy, a twofold increase in serum prolactin level followed true epileptic seizures, but no significant change followed pseudoepileptic attacks in 6 other patients. Serum prolactin level concentration is a useful biochemical marker to distinguish between epileptic and pseudoepileptic seizures**[8] Yerby MS, et al**, stated that "Serum prolactin level levels rise after generalized tonic-clonic and partial complex seizures, but not after pseudoepileptic seizures. The criteria for a significant elevation in serum prolactin level vary with individual investigators. The prevalence of pseudoseizures in the population studied determines the predictive value of serum prolactin level determinations. In populations where most patients have epilepsy, a rise in serum prolactin level is highly predictive for true epilepsy, but no increase in serum prolactin level is not predictive for pseudoseizures."**[9]**We categorized patients into 7 groups according to the etiology; infective/inflammatory (which includes meningitis, cerebral malaria, autoimmune encephalitis, viral encephalitis): metabolic encephalopathy (hypoglycemic encephalopathy, hypoxic encephalopathy, uremic encephalopathy) cerebrovascular accidents, hemorrhage (SAH, SDH, and EDH), seizure disorder, SOL(AV Malformation, cavernoma, brain abscess) and pseudo seizure and compared to serum prolactin level. In the first sample (within 20 minutes), there were total 49 patients of these 7 etiology i.e. in infective/inflammatory, CVA, hemorrhage, SOL, seizure disorder, PNES, encephalopathy with normal serum prolactin level and 51 of them with raised serum prolactin within 20minutes.In the group of encephalopathy there are 9 patients (18%) in prolactin normal level (<17) and 6 patients(40%) in serum prolactin level>=17 within 20 minutes. Hence association was present within the first 20 minutes only. Out of 15 patients in the group of infective/inflammatory there are 3 patients (6%) in prolactin normal level (<17ug/l) and 12 (23.52%) in serum prolactin level>=17ug/l within 20 minutes. So we observed that in patients with infective etiology there was association with serum prolactin level within 20 minutes and even after 24 hours, this may be due to the seizures or etiology itself. Out of 4 patients in the group of hemorrhage there are 1 patient (2%) had normal serum prolactin level (<17) and 3 patients (5%) in serum prolactin level>=17 within 20 minutes. The p value is 0.32, which is statistically insignificant. Out of 12 patients in the group of CVA there are 5 patients(10%) in prolactin normal level (<17) and 6 patients(11%) in serum prolactin level>=17 within 20 minutes. The p

value is 0.58, which is statistically insignificant. After 24 hours, in the 2nd sample of patients with CVA there were no patient with raised serum prolactin level. Our results were similar to **Sankalp Kumar Tripathi et al**concluded that Serum prolactin level was found significantly increased in patients of ischemic stroke (11.8ng/ml) as compared to controls (6.6 ng/ml) with a p value < 0.01 .**[10]** In our study out of 15 patients in the group of encephalopathy, 9 patients had prolactin level less than 17(p = 0.35NS). But in **Zhang GY et al** found that PRL levels were significantly higher in moderate and severe HIE neonates at the acute stage compared with those of controls and mild HIE neonates (P < 0.01). **[11]** Out of 20 patients in the group of seizure disorder there are 3(6%) in prolactin normal level (<17) and 17 (33.3%) in serum prolactin level>=17 within 20 minutes. The p value was 0.36, statistically insignificant. Hence association was present within the first 20 minutes only. Similarly **Tajammul Ehsan et al** suggested that the serum prolactin level may increase after epileptic seizures, but the increase is transient.[12]

**Willert et al 2004**, in their study concluded that a greater degree of increase in postictal serum prolactin level (measured at 10, 20,30minutes, 1 and 6hours) in patients with epileptic seizures compared with patients with PNES.**[13]**

**Morales A et al** found out in their study that Postictal prolactin levels were obtained 30 min after the seizure, and recovery levels were ascertained 2-4 days later. The ratio of postictal prolactin level to recovery baseline level (prolactin ratio) was used as an indicator of postictal prolactin increase. The specificity and sensitivity of a prolactin ratio of > 2 was compared with the current standard of diagnosis (seizure discharges recorded by ictal EEG**). [14]**

**Tomson T, et al** stated that "Prolactin levels were normal in all patients which indicates that, in contrast to single seizures, status epilepticus is not associated with an increase in serum prolactin level"**.[15]**

**Conclusions**

In our study we concluded that there was a increase in serum Prolactin level within 20 minutes of seizure in patients presenting with GTCS which returned to baseline after 24 hours of seizure free interval. We could not form an association in cases of focal seizure though there was a rise in serum Prolactin level in few cases within 20 minutes.

Pseudoseizure did not show rise in serum prolactin level within 20 minutes of abnormal body movement.

The rise in serum prolactin level within 20 minutes of seizure and abnormal EEG was not always related and no association could be formed.

As ours is a small study, it is difficult to establish serum prolactin as a diagnostic marker for seizure, but it is a strong predictor to differentiate true seizure from pseudoseizure.

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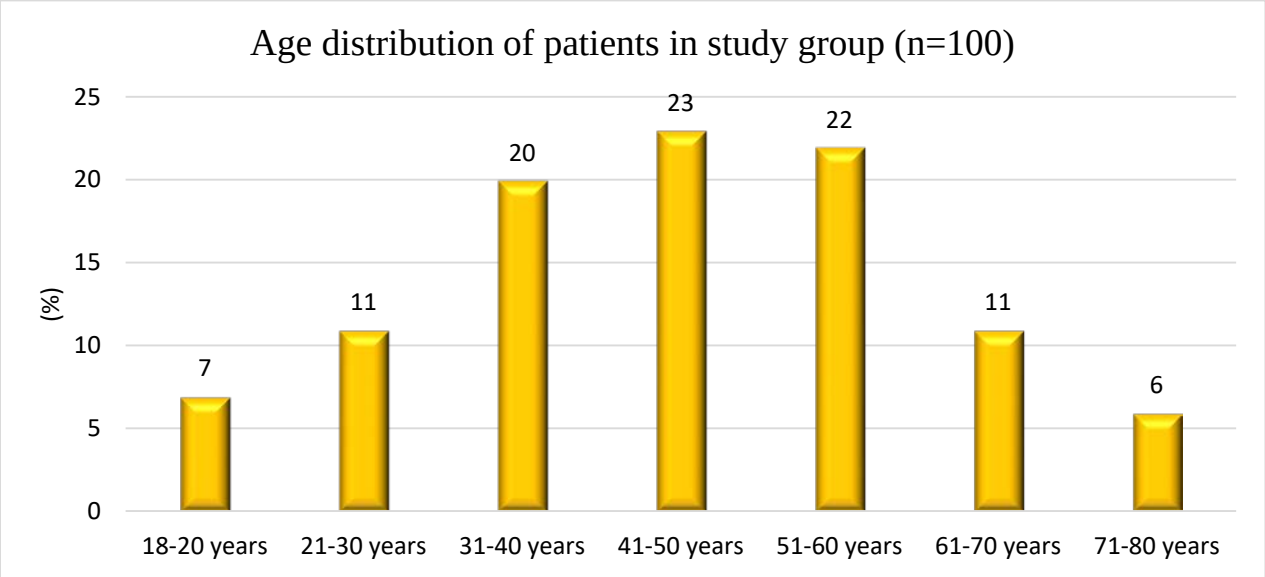
**Legend Figures and Tables**




The mean, median and mode of age distribution are 45 years.

Table 1:

| Type of seizure | Serum Prolactin Levels(ug/L) | | | | | |
|---|---|---|---|---|---|---|
| | At 20 min | | | After 24 hour | | |
| | ≤17 | >17 | P value | ≤17 | >17 | P value |
| Focal | 4 | 4 | 0.95 NS | 8 | 0 | 0.16 NS |
| GTCS | 20 | 46 | <0.0001 | 49 | 17 | 0.005 |
| Pseudo seizure | 25 | 1 | <0.0001 | 25 | 1 | 0.028 |

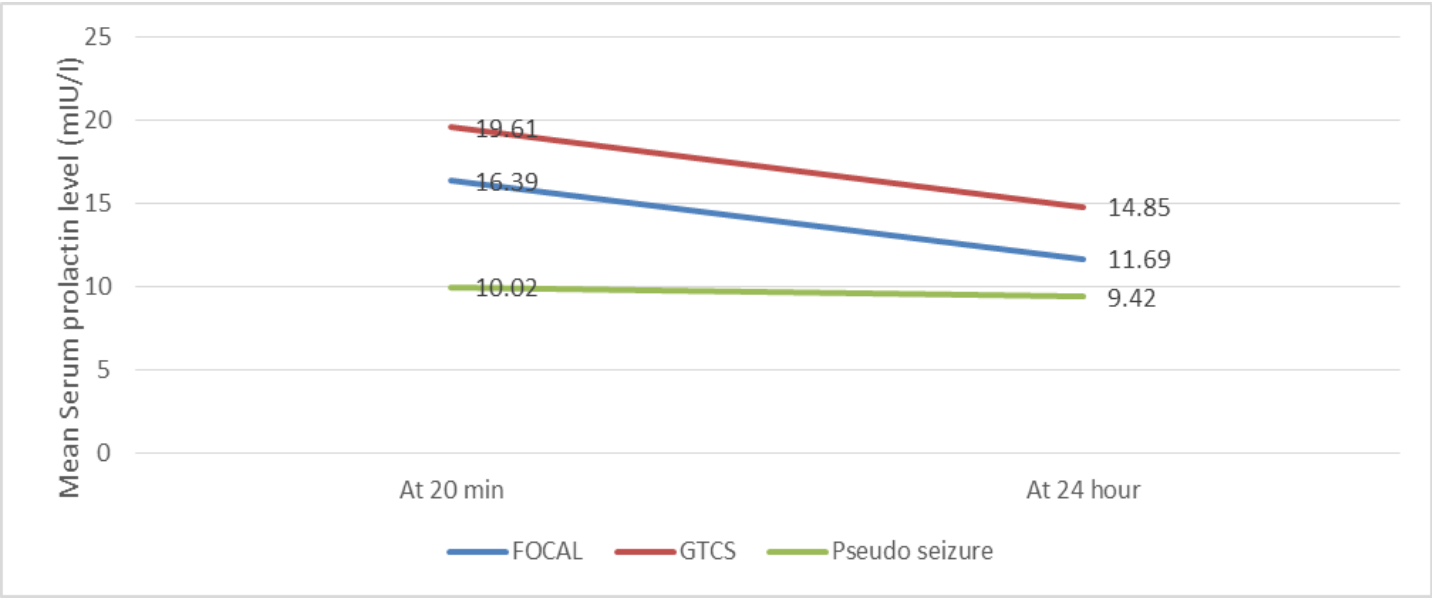
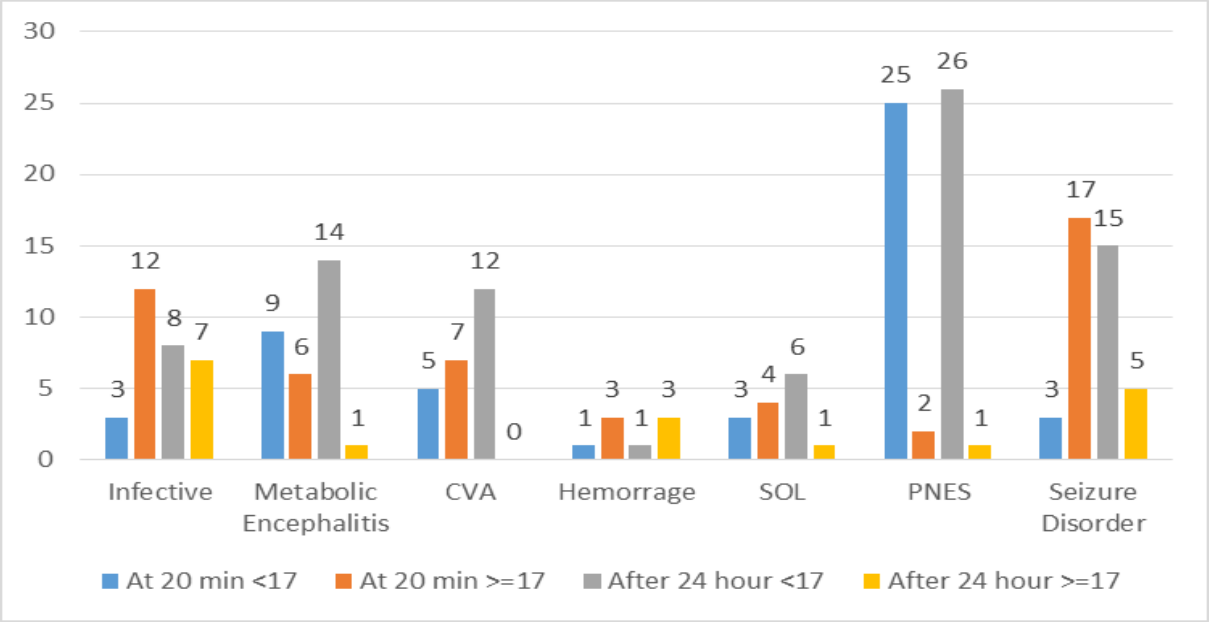


Table2: Etiology of seizure vs serum prolactin level within 20 mins and after 24 hours of seizure free interval in study group (n=100)

| Etiology | Serum Prolactin Levels(ug/L) | | | | | |
|---|---|---|---|---|---|---|
| | At 20 min | | | After 24 hour | | |
| | ≤17 | >17 | P value | ≤17 | >17 | P value |
| Infective/Inflammatory | 3 | 12 | 0.015 S | 8 | 7 | 0.0017 |
| Encephalopathy | 9 | 6 | 0.35 NS | 14 | 1 | 0.21 |
| CVA(ischemic /thrombosis) | 5 | 7 | 0.58 NS | 12 | 0 | 0.083 |
| Hemorrhage | 1 | 3 | 0.32 NS | 1 | 3 | 0.002 |
| SOL | 3 | 4 | 0.73 NS | 6 | 1 | 0.79 |
| PNES | 25 | 2 | <0.0001 | 26 | 1 | 0.023 |
| Seizure disorder | 3 | 17 | 0.0006 | 15 | 5 | 0.36 |

Seven different etiology of seizure are compared with serum prolactin in the study group (n=100)




Graphical representation of the rise of serum prolactin with etiology within 20 minutes and 24hours of last seizure in study group (n=100).