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Diagnostic role of serum prolactin level in different kinds of seizure and seizure-like episode in children: A hospital-based study

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ABSTRACT

Background: Serum prolactin level has been previously used in distinguishing epileptic seizure from non-epileptic seizure, as prolactin level usually rises following an epileptic seizure in children. **Aims and Objectives:** We conducted this study to determine the role of serum prolactin as a surrogate marker of seizure disorder and whether serum prolactin level varies between different types of seizure, febrile seizure, and seizure mimics. **Materials and Methods:** This cross-sectional comparative study was conducted for 1 year among 113 children between 6 months and 16 years of age of either sex. They were divided into 3 groups (1) epileptic seizure, (2) febrile seizure, and (3) seizure mimics. The blood sample was collected within 1 h of the occurrence of seizure for estimation of serum prolactin level. Each child was investigated and treated according to the protocol. **Results:** Mean post-ictal prolactin level was found significantly higher in epileptic seizure (29.94 ± 7.97 ng/mL) compared to febrile seizure (10.21 ± 0.94 ng/mL), and seizure mimics (8.73 ± 0.67 ng/mL). Among group 1, serum prolactin levels significantly elevated in children with generalized tonic-clonic seizure (GTCS) (34.18 ± 2.76 ng/mL) and complex partial seizure (CPS) (31.38 ± 1.59 ng/mL) compared to simple partial seizure (SPS) (14.36 ± 2.33 ng/mL). Post-ictal serum prolactin levels remain elevated for a longer duration in GTCS (54.26 ± 5.19 min) and CPS (45.19 ± 1.73 min) compared to children with SPS (26.76 ± 2.33 min). **Conclusion:** Estimation of serum prolactin level within 1 h after a seizure can be used for screening purposes to distinguish between epileptic and non-epileptic seizures. A high prolactin level is suggestive of GTCS or CPS whereas a low level is indicative of SPS, febrile convulsion, or seizure mimics with a prolactin cutoff taken 24 ng/mL in our study.

Key words: Children; Seizure disorder; Serum prolactin level

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INTRODUCTION

Seizure disorder is a broad term that includes epilepsy, febrile seizure, and other symptomatic seizures secondary to metabolic, infectious, or other causes. Since the diagnosis of epilepsy involves long-term management and carries a lot of social and psychological stigma, one needs to differentiate it from other common conditions resembling it. Misdiagnosis of seizure occurs in about 14% of cases as it is not always easy to establish the diagnosis of seizure.[1] Seizures can easily be confused with other diagnoses, such as syncope, migraine, or transient ischemic attack, but they are most frequently confused with non-epileptic seizures of psychogenic origin. A positive electroencephalography (EEG) is the gold standard for establishing the diagnosis of epilepsy and, in some cases, for evaluating seizure type and syndrome. In contrast, a negative EEG finding does not rule out the diagnosis of epilepsy. In developed countries, expensive, sophisticated, and time-consuming investigations such as 24-h video monitoring, ambulatory EEG, and provocative EEG tests are used in cases of diagnostic uncertainty.

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In India, such modalities are not easily available in every center and hence a cheaper and easily accessible alternative is required. Prolactin elevation in serum following seizure has been considered a potential candidate for a surrogate marker of seizure. Prolactin level may be of use in distinguishing epileptic seizure from non-epileptic seizure, as prolactin level usually rises following an epileptic seizure.[2] Although there are many studies evaluating prolactin levels in the post-ictal period for the differential diagnosis of epileptic from non-epileptic seizure, the studies done on children in India are limited. Hence the present study was done at our institution to assess the role of elevated levels of serum prolactin as a biochemical marker in the diagnosis of seizure disorder and to find out whether serum prolactin level can be used in differentiating various types of seizure disorder, febrile seizure and seizure-like event in children.

Aims and objectives

The specific objectives of this study were as follows: (1) to determine the role of serum prolactin level as a biochemical marker in the diagnosis of seizure disorder and (2) to find out whether serum prolactin level can be used in differentiating various types of seizure disorder, febrile seizure and seizure-like event in children.

MATERIALS AND METHODS

This hospital-based cross-sectional comparative study was done at the pediatric department of a district medical college and hospital for a period of 1 year, with 113 children between 6 months to 16 years of age of either sex who presented to the emergency department and were admitted to indoor with one or more episodes of seizure or seizure-like episode. The predicted sample size of 113 for this study was calculated using the formula $n=([Z\alpha+Z\beta]/C)^2+3$, where the standard normal deviate for $\alpha=Z_\alpha=1.96$, the standard normal deviate for $\beta=Z_\beta=1.282$ and $C=0.5*\ln([1+r])/[1-r])=0.3095$ to detect a moderate correlation ($r=0.30$) between serum prolactin level with diagnosis of seizure.

The study was conducted after obtaining informed and written consent from the parents of the children and necessary ethical clearance from the Institutional Ethics Committee.

Inclusion criteria

All children in the age group of 6 months to 16 years presented in emergency and were admitted indoors with seizure or seizure-like episodes, which occurred within the last 1 h were included.

Exclusion criteria

(1) Children having any metabolic disturbances, (2) those with infective central nervous system pathology, (3) those who have a structural neurological abnormality, and (4) those whose parents refused to give consent for this study were excluded.

Each child under the study was subjected to a detailed history, physical and neurological examination, relevant investigations, treatment according to the protocol, and follow-up. A thorough history was taken for age, mode of onset, number of seizures experienced, duration of seizure, state of the sensorium, any precipitating factor, febrile episode, drug intake, mental retardation, developmental milestones, birth history, any significant past medical or surgical illness, and history of similar illness in the family. Standard laboratory tests and imaging techniques such as magnetic resonance imaging (MRI) and EEG were done according to the protocol. Cases were then divided into 3 groups: Group 1: 38 cases with generalized tonic-clonic seizure (GTCS), complex partial seizure (CPS), or simple partial seizure (SPS) having a typical history of seizure with positive EEG findings. Group 2: 38 cases with a typical febrile seizure, Group 3: 37 cases with conditions mimicking seizure such as breath-holding spells, night terrors, syncope, pseudo seizure, etc. with normal EEG findings. Blood was collected within 1 h of occurrence of seizure for various routine and special investigations and 2 mL sample was sent to the Department of Biochemistry for estimation of serum prolactin level. In the present study, serum prolactin level was evaluated by double antibody sandwich technique using direct chemiluminescent method. We considered serum prolactin levels >24 ng/mL as high, as it is the upper limit of normal for all age groups in both sexes. The data of the enrolled cases were collected prospectively and for retrospective analysis, the data were compiled in the pre-designed pro forma.

Statistical analysis

Appropriate statistical software, including but not restricted to MS Excel. Statistical Package for the Social Sciences version 20 was used for statistical analysis. Graphical representation was done in MS Excel 2010. Quantitative data was presented with the help of mean and standard deviation. Comparison among the study group was done with the help of an unpaired "t" test as per the results of the normalcy test. Qualitative data was presented with the help of frequency and percentage tables. Association among the study groups is assessed with the help of the analysis of variance (ANOVA) test, Student "t" test, and Chi-square test, and $P<0.05$ were considered statistically significant.

RESULTS

Table 1 shows that the majority of the children in groups 1 and 3 (10.6% and 9.7%, respectively) were in the age group of 12–16 years whereas the majority of the children in group 2 (29.3%) were in the age group of 6 months–4 years.

The mean age of children in group 1 was 9.11±4.09 years whereas the mean age of children in group 2 and group 3 was 2.82±1.10 years and 9.07±4.71 years, respectively. There was a significant difference in the age of patients of different groups as per the ANOVA test (P<0.05). There were 22 (19.5%), 20 (17.7%), and 16 (14.1%) male children in group 1, group 2, and group 3, respectively, whereas female children constituted 14.1%, 15.9%, and 18.7% of our study groups, respectively. There was no significant difference in the gender of patients of different groups as per the Chi-square test (P>0.05).

Table 2 shows that, out of 38 cases, 23 (60.5%) children had GTCS, whereas 8 (21.1%) and 7 (18.4%) children had CPS and SPS, respectively. Out of those mean post-ictal prolactin level was significantly higher in children with GTCS (34.18±2.76ng/mL) and CPS (31.38±1.59 ng/mL) compared to children with SPS (14.36±2.33 ng/mL) as per Student t-test (P<0.05).

Table 3 shows that the mean post-ictal prolactin level was significantly higher in epileptic seizure (group 1; 29.94±7.97 ng/mL) compared to febrile seizure (group 2; 10.21±0.94 ng/mL), and seizure-like episodes (group 3; 8.73±0.67 ng/mL) as per Student t-test (P<0.05).

Table 4 shows that the mean post-ictal duration up to which high serum prolactin was detected was significantly higher in group 1 (48.03±11.48 min) compared to group 2 (29.09±13.05 min) and group 3 (18.67±227 min) as per Student t-test (P<0.05).

Table 5 shows that the mean post-ictal duration with high prolactin levels was significantly higher in children with GTCS (54.26±5.19 min) and CPS (45.19±1.73 min) compared to children with SPS (26.76±2.33 min) as per Student t-test (P<0.05).

DISCUSSION

Seizure is among the most common neurological problems in children and the most common neurological emergency attended by pediatricians. It is an excessive hypersynchronous electrical discharge from an aggregate of central nervous system neurons and each burst of electrical activity is called a seizure. A seizure arising from the motor cortex leading to abnormal motor activity is called convulsion and epilepsy is defined as "two or more unprovoked seizures occurring at an interval of more than 24 h apart."[3] Less than one-third of seizures develop into epilepsy. The cumulative lifetime incidence of epilepsy is 3% where more than half of the cases begin in childhood. A recent meta-analysis shows that the overall prevalence rate of epilepsy in India at 5.59/1,000 population and the worldwide prevalence of epilepsy is 4–10/1,000 population.[4] Major advances in the understanding and treatment of epilepsy have occurred in the last century, and research has been carried out on the epidemiological, diagnostic, and social aspects of the disorder. MRI, EEG, long-term EEG monitoring, and video-EEG registration are useful diagnostic tools. Unfortunately, in developing countries like India, these facilities are not available in every center, so it would be very helpful to identify another surrogate marker of seizure. The first study to evaluate the correlation between serum prolactin elevation and epilepsy was published in 1978 by Trimble, who showed that a generalized tonic-clonic seizure increased prolactin serum level but psychogenic non-epileptic seizures did not.[5] EEG in pediatric patients is extremely difficult if the child is struggling, and sedation may lead to a change in the character of waves and hence the interpretation of EEG could be difficult. Conditions mimicking seizures are often mistaken for epilepsy but do not have the characteristic EEG changes that accompany a true epileptic seizure. Here comes the probable role of serum prolactin level after seizures. Prolactin is a hormone that is secreted in a pulsatile manner from the anterior pituitary gland and is under inhibitory control from the hypothalamus, by dopamine-mediated suppression of prolactin release. Prolactin level rises after exercise, high protein diet, minor surgical procedure, and following epileptic seizures.[6]

In our study, both the incidence of true seizure (group 1) and seizure-like episodes (group 3) are more prevalent in the age group of 4–16 years whereas febrile convulsion

Table 1: Distribution of children in three groups according to age and gender

Demographic profile	Group 1 (n=38)		Group 2 (n=38)		Group 3(n=37)		Total (n=113)		P-value
	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage	
Age group									<0.05
6 months–4 years	6	5.3	33	29.3	6	5.3	45	39.9	
>4–8 years	9	7.9	5	4.4	10	8.9	24	21.2	
>8–12 years	11	9.7	0	0	10	8.9	21	18.6	
>12–16 years	12	10.6	0	0	11	9.7	23	20.3	
Mean age	9.11±4.09		2.82±1.10		9.07±4.71		6.98±4.68		
Gender									
Male	22	19.5	20	17.7	16	14.1	58	51.3	>0.05
Female	16	14.1	18	15.9	21	18.7	55	48.7	

Table 2: Comparison of post-ictal prolactin level between different types of seizure in group 1

Type of seizure	Total no (n=38)	Prolactin level (ng/mL)		P-value
		Mean	SD	
GTCS	23 (60.5%)	34.18	2.76	<0.05
CPS	08 (21.1%)	31.38	1.59	
SPS	07 (18.4%)	14.36	2.33	

SD: Standard deviation, GTCS: Generalized tonic-clonic seizure, CPS: complex partial seizure, SPS: Simple partial seizure

Table 3: Comparison of post-ictal prolactin levels between different groups

Patient group	Prolactin level (ng/mL)		P-value
	Mean	SD	
Group 1	29.94	7.97	<0.05
Group 2	10.21	0.94	
Group 3	8.73	0.67	

SD: Standard deviation

Table 4: Maximum duration of stay of high prolactin level after different types of seizures or seizure-like events (in minute)

Group distribution	Maximum duration (in minute) of high prolactin level		P-value
	Mean	SD	
Group 1	48.03	11.48	<0.05
Group 2	29.09	13.05	
Group 3	18.67	2.27	

SD: Standard deviation

Table 5: Maximum duration of stay of high prolactin level after different types of seizures in group 1 (in min)

Type of seizure	Maximum duration (in min) of high prolactin level		P-value
	Mean	SD	
GTCS	54.26	5.19	<0.05
CPS	45.19	11.73	
SPS	26.76	2.33	

SD: Standard deviation, GTCS: Generalized tonic-clonic seizure, CPS: Complex partial seizure, SPS: Simple partial seizure

(group 2) is more prevalent below 4 years of age. This age preponderance is matching with the normal expected age group of such episodes and is similar to the studies of Mangunsong, Banerjee et al., and Çitilcioğlu et al.,[7-9] In the present study, 60.5% of children in group 1 had GTCS whereas 21.1% and 18.4% children had CPS and SPS, respectively, which is consistent with the study of Mishra and Chaudhary.[10] In the 3rd group with seizure-like episodes, 48.6% had pseudo-seizures, and 27.1%,16.2%, and 8.1% children had breath-holding spells, night terrors, and syncope, respectively. This is comparable to the studies of Mangunsong, Banerjee et al., and Çitilcioğlu et al.[7-9]

In the present study, the mean post-ictal prolactin levels were significantly higher in group 1 (29.94±7.97 ng/mL) compared to group 2 (10.21±0.94 ng/mL), and group 3 (8.73±0.67 ng/mL). This is concordant with the studies of Mangunsong, Banerjee et al., and Mishra et al.[7,8,10] Mangunsong study determining the diagnostic potential of serum prolactin levels as an alternative diagnostic tool for children with seizures reported post-ictal serum prolactin level significantly higher in the epileptiform EEG group. The mean serum prolactin levels were 23.78 ng/mL and 10.57 ng/mL in patients with epilepsy and non-epilepsy, respectively, using a prolactin cutoff point of 17.2 ng/mL.[7] Mahendrappa et al. found in their study that there is a significant rise in serum prolactin level in children with epileptic seizures compared to febrile seizures if measured within 3 h of occurrence of seizures.[11]

In our study, the mean post-ictal prolactin levels were significantly higher in children with GTCS (34.18±2.76 ng/mL) and CPS (31.38±1.59 ng/mL) compared to children with SPS (14.36±2.33 ng/mL), with similar observations noted by Mangunsong and Banerjee et al., in their studies.[7,8] Banerjee et al. study reported mean prolactin values significantly higher in GTCS (34.46 ng/mL) and CPS (31.60 ng/mL) compared to SPS (14.20 ng/mL).[8] Eighty percent of GTCS, 60% of CPS, and 20% of SPS had elevated levels with sensitivity and specificity of elevated prolactin level as an indicator of an epileptic seizure 64% and 98%. respectively. Chen et al. study on the use of serum prolactin as a diagnostic marker of epilepsy reported its sensitivity higher for generalized tonic-clonic seizures (60.0%) than for CPS (46.1%).[12] Mishra et al. study determining the role of serum prolactin level in different types of seizures and seizure-like activity in children observed higher mean prolactin levels in GTCS (37.27 ng/mL) and CPS (31.44 ng/mL) as compared to SPS (17.99 ng/mL).[10]

It was observed in the present study that the mean post-ictal duration up to which prolactin level was found elevated was significantly higher in group 1 (48.03±11.48 min) compared to group 2 (29.09±13.05 min) and group 3 (18.67±227 min). This is in concordance with the studies of Mangunsong and Çitilcioğlu et al.,[7,9] Çitilcioğlu et al. a study in children observed the 10 min serum prolactin levels significantly higher in an epileptic group compared to non-epileptic-seizures-group, but there was no statistically significant difference between groups if serum prolactin measured at 60 min.[9] In our study, mean post-ictal prolactin levels remain significantly higher for a longer duration in children with GTCS (54.26±5.19 min) and CPS (45.19±1.73 min) compared to children with SPS (26.76±2.33 min). Similar observations were noted by Banerjee et al., Mangunsong, Mishra and Chaudhary, and Chen et al.,[7,8,10,12,13] Banerjee et al. study observed a definite correlation between the post-ictal level of elevated prolactin and its duration only in the cases of GTCS.[8] It was observed that the highest level was attained 10 min post-ictal with a

progressive decline attaining a normal level in all cases with a post-ictal duration of more than 100 min.

Limitations of the study

This is a single-center study with a small number of samples. A multicenter study with a larger sample size is needed before concluding that we can depend on serum prolactin level as a diagnostic tool for early detection of seizure. Second, not all the centers have the facility for serum prolactin estimation and this test is limited to positive diagnosis only, normal value of serum prolactin does not rule out seizures always.

CONCLUSION

Estimation of serum prolactin level within 1 h after a seizure can be used for screening purposes to distinguish between epileptic and non-epileptic seizures. A high prolactin level is suggestive of GTCS or CPS whereas a low level is indicative of SPS, febrile convulsion, or seizure mimics with a prolactin cutoff of 24 ng/mL in our study. Levels of prolactin remain elevated for a longer duration in GTCS and CPS compared to other types before gradual taper with lapsed time between seizure and blood sampling. Although it cannot be used exclusively for differentiation between subtypes of epileptic seizures, it can easily be applied in cases of diagnostic uncertainly between epileptic and non-epileptic events, before going to more sophisticated and expensive investigations. Hence, we can use this surrogate marker of epilepsy as a fairly reliable tool for early diagnosis before confirming the final diagnosis by EEG.

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REFERENCES

1. Sridharan R and Murthy BN. Prevalence and pattern of epilepsy in India. Epilepsia. 1999;40(5):631-636. https://doi.org/10.1111/j.1528-1157.1999.tb05566.x
2. Anzola GP. Predictivity of plasma prolactin levels in differentiating epilepsy from pseudoseizures: A prospective study. Epilepsia. 1993;34(6):1044-1048. https://doi.org/10.1111/j.1528-1157.1993.tb02132.x
3. Pal DK. Epilepsy control in the 21st century: Leave no child behind. Epilepsia. 2003;44(3):273-275. https://doi.org/10.1046/j.1528-1157.2003.52202.x
4. Bharucha NE. Epidemiology of epilepsy in India. Epilepsia. 2003;44 Suppl 1:9-11. https://doi.org/10.1046/j.1528-1157.44.s.1.5.x
5. Trimble MR. Serum prolactin in epilepsy and hysteria. Br Med J. 1978;2(6153):1682. https://doi.org/10.1136/bmj.2.6153.1682
6. Mellers JD. The approach to patients with "non-epileptic seizures". Postgrad Med J. 2005;81(958):498-504. https://doi.org/10.1136/pgmj.2004.029785
7. Mangunsong H. Serum prolactin for differentiating epileptic seizures in children. Paediatr Indones. 2015;55(5):273-276. https://doi.org/10.14238/pi55.5.2015.273-6
8. Banerjee S, Paul P and Talib VJ. Serum prolactin in seizure disorders. Indian Pediatr. 2004;41(8):827-831.
9. Çitilcioğlu HB, Matyar S, Akgül O, Bucak IH and Turget M. Serum prolactin levels in differential diagnosis of pediatric epileptic and nonepileptic (pseudo-SEIZURES) seizures. Paediatr Croat. 2015;59:203-207. https://doi.org/10.13112/PC.2015.30
10. Mishra R and Chaudhary BN. Study of the levels of serum prolactin in childhood seizure disorder. IOSR J Dent Med Sci (IOSR-JDMS). 2017;16(5):48-50. https://doi.org/10.9790/0853-1605094850
11. Mahendrappa KB, Sathya SP and Suma MN. Serum prolactin level in children with febrile seizure and epileptic seizure; comparative study. J Nepal Paediatr Soc. 2017;37(1):67-71. https://doi.org/10.3126/jnps.v37i1.16502
12. Chen DK, So YT, Fisher RS and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Use of serum prolactin in diagnosing epileptic seizures: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2005;65(5):668-675. https://doi.org/10.1212/01.wnl.0000178391.96957.d0
13. Chaudhary BN and Mishra R. Role of serum prolactin levels in differentiate childhood seizure episodes and conditions mimicking seizure episodes. IOSR J Dent Med Sci (IOSR-JDMS). 2017;16(12):54-57. https://doi.org/10.9790/0853-1612095457

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PK, SP- Concept and design of the study, review of literature; **AK, SM-** Data acquisition, statistical analysis; **SL-** Manuscript writing, manuscript editing; **MRS-** Critical revision of the manuscript.

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