Serum Prolactin Level in Children with Febrile Seizure and Epileptic Seizure; Comparative Study

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Abstract

Introduction: Transient hyperprolactinaemia has been reported to follow unprovoked seizures, a finding proposed to be useful in the differential diagnosis of epilepsy. On this basis we conducted a study with an objective to compare the postictal serum prolactin level in children with febrile seizures (FS) and epileptic seizures (ES) to evaluate, whether serum prolactin (PL) could be used a predictor in the diagnosis of ES. **Material and Methods:** This was a prospective comparative study was conducted on 52 children (26 in febrile seizures group and 26 in epileptic seizure group) in the age group of six months to five years. Children with CNS infection, developmental delay, structural CNS defects or neurological abnormality, metabolic disorders and those on drugs, known to have altered serum prolactin level were excluded. Blood for estimation of serum prolactin was collected within 180 minutes of occurrence of seizure. Level of serum prolactin was quantitatively assayed by chemiluminescence method and the levels were considered high, if values were greater than 23 ng/ml, which is the upper limit of normal for all age groups and both sex. **Results:** The mean serum prolactin level in epileptic seizures group was 25 ng/ml and that of febrile seizures group was 10.72 ng/ml. High level of serum prolactin was noted in 17 children (77.2%) with GTCS and 3 children (75%) with CPS. None of the children with febrile seizures had significant raise in the level of serum prolactin. **Conclusion:** There is a significant rise in serum prolactin level in children with epileptic seizures compared to febrile seizures, if measured within 3 hours of occurrence of seizures. Thus, the post-ictal serum prolactin level can be used as an additional investigation to diagnose or predict epileptic seizures in children.

Key words: Postictal period, Serum prolactin level, febrile seizure, epileptic seizure.

Introduction

It has been shown that during generalized tonic, clonic seizure and most complex partial seizures, which originate in the temporal lobe, the spread of electrical activity from the ventromedial hypothalamus and medial temporal structures leads to release of a specific prolactin

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regulator into the hypophyseal portal system and consequently an increase in prolactin[1]. There is also evidence that patients with unprovoked seizures may have high baseline PL levels, which could be of value in predicting epilepsy after a first convulsive attack[2,3]. The incidence of FC in children below the age of five years is about 2-4 %[4]. Mittal, in his study, has reported the incidence of FS as high as 10.3%[5]. Uncertainty of diagnosis arises, when seizure has occurred in isolation or the description is unreliable. Jeavons and co-workers showed that 20% of children treated as having epilepsy did not actually have the disease[6]. So there is a need to assess the value of serum PL level in differentiating FS from ES. We aimed to analyze the association between serum PL levels in ES versus FS.

Materials and Methods

A prospective comparative study was conducted on 52 children in the age group of six months to five years. Children admitted within three hours of occurrence of seizures and with duration of seizure less than 30 minutes were included in the study. Among various types of ES, generalized tonic clonic seizures (GTCS), complex partial seizure (CPS) and simple partial seizures were included in the study. Children with CNS infection, developmental delay, structural CNS defects or neurological abnormality, myoclonic or absence seizures, metabolic disorders and patients on drugs like antihistamines, metaclopromide, insulin, ranitidine which are known to alter PL level were excluded.

Out of 96 epileptic seizure cases admitted during the study period, 26 cases meeting the inclusion criteria were grouped in ES group I, and equal numbers of age matched children with FS were included in group II.

According to ILAE, the definition of an ES is “a transient occurrence of signs and /or symptoms due to abnormal excessive or synchronous neuronal activity in brain” [7].

Definition of GTCS-ICD-10 CODE G40.3, with criteria: Generalised tonic and clonic movements associated loss of consciousness, postictal drowsiness. CPS- ICD-10 CODE G40.2, with criteria; asynchronous clonic or tonic movements, with/without aura, with/without automatisms, associated altered state of consciousness. SPS-ICD-10 CODE G40.1, with criteria: asynchronous tonic/clonic movements, consciousness retained no automatism, no postictal drowsiness. Febrile seizures-ICD-10 CODE R56.0, with the criteria: Age between six months to five years, fever more than 38.5°C (measured using mercury thermometer kept for 5 minutes at the axilla), neuro-infection ruled out.

After Ethical Committee clearance and informed consent from parents, data was collected as per the proforma. The exact interval of time between occurrence of seizures and presentation to the hospital was noted. Blood sample was collected under strict aseptic precautions in children admitted within three hours of occurrence of seizures and level of serum PL was quantitatively assayed by chemiluminescence method. PL levels were considered high, if values are greater than 23 ng/ml, which is the upper limit of normal for all age groups and both sexes[2].

Other investigations like hematological, biochemical, CSF analysis and EEG were done in all cases to rule out associated abnormalities. The data was analyzed using appropriate statistical methods. The data entry was done in Microsoft excel work sheet and all the statistical analyses were carried out using EPI-INFO package version 3.5.3.

Results

The present study was conducted in the Department of Paediatrics, in a Medical College, south India. During the study period, total number of admission to the pediatric department was 5898, out of which 659 (11.1%) cases were admitted for seizures, 316 (5.3%) were diagnosed as FS, 96 (1.6%) had ES and remaining 247 (4.1%) had other causes for seizure. Out of 96 epileptic seizure cases admitted during the study period, 26 cases met the inclusion criteria and were grouped in ES, group I and equal numbers of age matched children with FS were included in group II.

Sex wise, there were 10 male and 16 female children in FS group and 11 male and 15 female children in ES group. P value is 0.775, which is statistically not significant. In FS group all 26 cases had GTCS, where as in ES group 22 had GTCS and 4 had CPS.

There was no statistically significant difference in the mean serum PL level in female and male children in both FS and ES group. (Mean serum PL level in FS group was 10.5 ng/ml in female and 11.1 ng/ml that of male children, with a p value of 0.7115, and in the ES group, the mean serum PL level in male children was 26.2 ng/ml and that of female children was 24.2 ng/ml with a *p*-value is 0.4136).

Out of six children with ES, having serum PL<23ng/ml, 5 (83.34%) had abnormal E.E.G findings and 1 (16.6%) had normal E.E.G findings. In FS group EEG was within normal limits in all children. In ES group, 17 children had abnormal EEG and 9 cases had normal EEG. The *p*-value is 0.0000, which is statistically significant.

Table 1: Age distribution of cases

Age group	Febrile seizures group		Epileptic seizure group	
	Number	Percentage (%)	Number	Percentage (%)
6 months -1year	8	30.8	6	23.1
>1 year - 2 years	13	50.0	7	26.9
>2 years - 5 years	5	19.2	13	50.0
Total	**26**	**100.0**	**26**	**100.0**

Table 2: Mean serum prolactin level in febrile seizure and epileptic seizure group

Patient group	Number	Mean Prolactin level (ng/ml)	SD	*p*-value	Student's t-teat
Febrile Seizure	26	10.72	3.66	0.0000	10.34
Epileptic Seizure	26	25.00	6.01	-	-

Table 3: Comparison of cases with significant serum prolactin level in both the groups

Prolactin status	Febrile seizures group		Epileptic seizure group	
	No.	%	No.	%
<23 (ng/ml)	26	100.0	6	3.1
>23 (ng/ml)	0	0.00	20	76.9
Total	26	100.0	26	100.0
$\chi 2$		32.50		
p-value		0.0000		

Table 4: Comparison of E.E.G with significant prolactin level in epileptic seizure group

Prolactin status	Normal EEG		Abnormal EEG	
	No.	%	No.	%
<23 (ng/ml)	1	11.1	5	29.4
>23 (ng/ml)	8	88.9	12	70.6
Total	9	100.0	17	100.0
$\chi 2$		1.11		
p-value		0.2957		

Discussion

The prevalence of epilepsy, as reported in a Meta analysis from South India is 5.59/1000 [8]. Globally, 10.5 million children aged 0-14 years are estimated to have active epilepsy, constituting 25% of the global epilepsy population[9,10]. In the United States and Western Europe epilepsy occur in 2% to 4% of all children[11]. The risk of developing epilepsy after a simple febrile seizure is low (1.5-2.4%) and therefore do not need further investigation or treatment[6].

In the present study, serum PL level was > 23 ng/ml in 20 (76.9%) children with ES and none of the children with FS had significant raise in the level of serum PL. There is no significant difference in serum PL level between the male and female children in both the groups. There was no abnormal E.E.G finding noted in children with FS group. In ES group, majority of children (60%) with serum PL > 23 ng/ml, had abnormal E.E.G finding and 8 (40%) had normal E.E.G findings, indicating a direct correlation between abnormal EEG findings and elevated serum PL level in children with ES. In the present study, the mean serum PL level in epileptic seizure group was 25.00 ng /ml and that of febrile seizure group was 10.72 ng /ml.

This is comparable to the study conducted by Banerjee S et al[2], who has noted the mean serum PL level 29.84 ng/ml in epileptic seizure and 10.52 ng/ml in febrile groups of children between 6 months to 12 years. In a similar study, Macooie et al, have noted, higher PL level of 47.42 ng/ml in ES group compared to 25 ng/ml in the present study and serum PL level of 18.78 ng/ml in the FS group, compared to 10.72 ng/ml in the present study[6]. In another study by Singh et al, there was significant raise of serum PL in ES group (28.6±2.3 ng/ml) compared to nonepileptic group[12].

Significantly elevated serum PL level in ES group was also noted by Bye et al, compared to nonepileptic group, indicating a definite correlation between epilepsy

and elevated PL level[13]. Vukmir in his study concluded that an elevated serum PL is a reliable confirmatory test, for epilepsy compared to febrile seizure[14].

Dirik and co-workers measured post-ictal serum PL and cortisol levels in 37 children with ES group, FS group and syncopal attack and in 37 normal controls[15]. They found significantly higher serum PL levels in the ES group. In typical FS, sub-clinical electrical activity does not exist, since the after-discharges are less intense and transient to project to the ventromedial hypothalamus, whereas, conditions mimicking seizures completely lack electrical discharges, which accounts for lack of PL elevation in conditions mimicking seizures[16]**.** In a study conducted by Banerjee et al[2], 80% of children with GTCS and 60% with CPS had elevated serum PL level. This result is comparable to the present study, where in 77.2% children with GTCS and 75% with CPS had elevated serum PL levels. Similar results were observed in a study conducted by Bye et al[13], where 80% of children with GTCS and 60% of children with CPS had elevated serum PL level. In the present study none of the children with FS group had elevated serum PL level which is comparable to the study conducted by Banerjee et al, who studied 75 children with GTCS, CPS, SPS, and FS and compared the serum PL level in children with various types of seizure[2].

It has been suggested that, when ictal discharges spread from the medial temporal structures to the hypothalamic nuclei, they also lead to an alteration in consciousness. This probably explains, why more cases of GTCS and CPS had elevated levels of PL[17]. Shah and colleagues analyzed the time lapse between the time of seizure and blood sampling on serum PL level and observed an inverse correlation between seizure and time lapse between the seizure event and blood sampling[18]. Singh et al, estimated the serum PL within 20 minutes of occurrence of seizure[12]. Anzola, has done serum PL within 60 minutes of postictal period and noted a significant increase (mean, 40 ng/ml) in serum PL in children with epilepsy group compared to nonepileptic group[19].

Banerjee et al[2] and Macooie et al[6]. estimated serum PL level within 120 minutes of occurrence of seizure. In our study, we estimated serum PL within 180 minutes of occurrence of seizure**,** which is similar to the study conducted by Bye et al[13]. Fein et al[20]. had used age matched levels of serum PL as cutoff value instead of single cut off value 23ng/ml. [20] The cut-off value of 23 ng/ml for elevated serum PL level is considered by many authors like Banerjee et al[2], Macooie et al,[6] and Bye et al[13]. Accordingly, the same cutoff value of 23 ng /ml is taken as the upper limit of normal in the present study. The level of PL may vary at different time of the postictal period. However, serial measurement of PL during the postictal period was out of the scope of this study.

Conclusion

The serum prolactin level was significantly raised in children with epileptic seizures compared to febrile seizures, when measured within three hours of occurrence of seizures. Thus, the post-ictal serum prolactin level can be used as an additional tool to diagnose epileptic seizures and exclude febrile seizures in children. Many more studies with serial measurements of serum prolactin levels at different time intervals of postictal period and a long term follow up of these children may be useful to know diagnostic value of serum prolactin level.

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