Role of Serum Prolactin Levels in Diagnosis of Epileptic and Pseudoepileptic Events in Children, A Tertiary Care Experience

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ABSTRACT

Introduction: Transient elevation of serum prolactin levels occurs in immediate postictal period in true epileptic events only. Current study was aimed to investigate the role of post-ictal serum prolactin levels in differentiation of true seizures from pseudo epileptic events.

Material and methods: A total of 110 patients of either sex between ages of 6 months to 12 years out of 676 cases admitted for seizure evaluation were enrolled in our study and divided into four groups. Group 1 included 30 children having frank seizures, group 2 included 30 children with typical febrile seizures, group 3 included 25 children with seizure mimics and group 4 included 25 children without seizures.The serum prolactin levels were quantitatively determined by using Coat-A-Count Prolactin Immuno-radiometric assay (IRMA). All data was analyzed by standard statistical methods.

Results: There were 64(58.2%) males and 46(41.8%) females with mean age of 60.8 and 61.3 months. The serum prolactin level was highest in group I with mean level of 25.5ng/ml ±10 SD(p value =0.00).The serum prolactin levels were raised in 30.3% (20/66) of patients in group I,II,and III when serum sample was obtained within 20 minutes and in none 0/19 (0.00%) when sample was taken after 20 minutes (p value =0.006).All patients with generalized tonic clonic seizures with abnormal EEG had abnormal prolactin levels while as only 83.3% with complex partial seizures and 20% with simple partial seizures had raised prolactin levels (p value =0.002).

Conclusion: There was a significant rise in serum prolactin level in children with epileptic seizures as compared to febrile seizures and seizure like events.

Keywords: Prolactin, Seizures

INTRODUCTION

Epilepsy is one of the most common neurological diseases, affecting 50 million people worldwide. It is defined as a susceptibility to recurrent seizures without precipitating factors. Epileptic seizures result from abnormal excessive or synchronous discharge in the brain. The prevalence of active epilepsy is approximately 1%, but 8 - 10% of the population has at least one seizure during their lifetime. Worldwide, it is estimated that 10.5 million children under 15 years have active epilepsy, representing about 25% of the global epilepsy population. Of the 3.5 million people who develop epilepsy annually, 40% are younger than 15 years, and more than 80% live in developing countries.[1] The adverse effects of anticonvulsant drugs, duration and expense of therapy and social implications, make it essential for accurate diagnosis, before starting treatment.[2]An elaborate history and accurate description is necessary for making correct diagnoses of seizures. Uncertainty arises when it has occurred in isolation or the description is unreliable. The repertoire of seizures is so extensive that even physicians find it difficult to distinguish between seizures and similar conditions.[2] EEG findings may be normal, nonpathognomic or inconclusive. In developed countries, expensive, sophisticated and time consuming investigations like 24-hr video monitoring, ambulatory EEG, provocative EEG tests and SPECT are used in cases of diagnostic uncertainty. However, they are not always conclusive. In India, such modalities are not easily available and hence a cheaper and easily accessible alternative is required.[2] 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 regulator into the hypophyseal portal system and consequently an increase in Prolactin. There is also evidence that patients with unprovoked seizures may have high baseline Prolactin levels, which could be of value in predicting epilepsy after a first convulsive attack.[3]

The diagnosis of epilepsy is essentially clinical. In the differential diagnosis of paroxysmal non-epileptic conditions mistaken for epilepsy, pseudo-epileptic seizures pose special problems and are a common manifestation of hysteria particularly in developing countries. Although numerous features have been compiled to distinguish pseudo-epileptic seizures from epilepsy, it is still not possible to make this distinction with certainty. In one study, the accuracy of clinical diagnosis ranged from 60% (for physicians referring patients for evaluation) to 72% (for neurologists viewing video-taped analyses of seizures, without knowledge of the

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How to cite this article: Rehana, Kaisar Ahmad, Mohd Irshad, Mohd Ashraf. Role of serum prolactin levels in diagnosis of epileptic and pseudoepileptic events in children, a tertiary care experience. International Journal of Contemporary Medical Research 2019;6(6):F11-F15.

DOI: http://dx.doi.org/10.21276/ijcmr.2019.6.6.50

clinical details or the accompanying electroencephalogram). The greatest difficulty in diagnosis is caused by complex partial seizures. Additional difficulties are caused by the co-existence of pseudo-epileptic seizures in 12% to 65% of patients with a' past or a concurrent history of epilepsy.

A biochemical marker of epileptic seizures would therefore be of considerable clinical use.[4] Such misdiagnosis occurs as the seizures are quite real, and people who have them do not have conscious, voluntary control over them. They are "false" only in that they have no physical cause or any focal discharge in brain; rather, they are psychological or physical reactions to stressful situations. Although their causes are different, "pseudoseizures" definitely resemble epileptic seizures and often it's difficult to tell the difference.[5]

Prolactin is secreted from the anterior pituitary gland and is inhibited by tubero-infundibular dopamine neurons in the arcuate nucleus of the hypothalamus. Abnormal electrical discharge passing through the hypothalamus may disrupt the normal functioning. Generalized neuronal discharge of a seizure stimulates the hypothalamus either directly through specific neurotransmitter changes (decrease in GABA and dopaminergic system) or through the release of other substances, thereby, causing increase in serum prolactin level during epileptic form of seizures. Acute changes in serum prolactin levels which occurred following some of the seizures may be useful in differentiating epileptic seizures from non epileptic seizures.[6]

This study was designed to find role of serum prolactin in diagnosis of various seizure types, pseudo seizures and its correlation with EEG findings.

MATERIAL AND METHODS

This prospective case control study was done in the department of pediatrics of Government medical college Srinagar in collaboration with department of immunology SKIMS after ethical clearance from ethical committee of Government medical college Srinagar. A total of 110 patients of either sex between ages of 6 months to 12 years out of 676 cases admitted for seizure evaluation between October 2008 to September 2009 were enrolled in our study after excluding cases like metabolic, infective, developmental, structural central nervous system disorders and those on drugs known to alter serum prolactin levels. The enrolled patients were divided into four groups after thorough history and examination. Group 1 included 30 children having frank seizures, group 2 included 30 children with typical febrile seizures, group 3 included 25 children with seizure mimics without having true seizures and group 4 included 25 children admitted for reasons other than seizures.3ml of venous blood was collected for determining serum prolactin in first three groups within first two hours of the event while as it was obtained between 9am to 12 noon in group 4.Sampling was repeated in group 1 after two hours. The serum prolactin levels were quantitatively determined by using Coat-A-Count Prolactin Immuno-radiometric assay (IRMA) in the department of immunology at SKIMS.All data was analyzed by standard statistical methods.

RESULTS

The age and gender distribution of our cases is shown in table 1. The different diagnosis in study groups are shown in table 2.

It was observed that the prolactin level was significantly high ($p = 0.000$) only within group I. In group I maximum prolactin level obtained was 40.5ng/ml and minimum prolactin level was 8ng/ml. Mean prolactin level for Group I was 25.5±10 SD. For Group II maximum prolactin level obtained was 22.5ng/ml, minimum was 2.3ng/ml and mean level was 9.4ng/ml ± 5.5 SD. In Group III maximum level was 15.5ng/ml and minimum was 1.5ng/ml and mean 7.8±3.8 SD. In Group IV maximum prolactin level was 20ng/ml, minimum was 2.0 ng/ml and mean level was 7.4ng/ml ± 5.2 SD.

Gender	N	min	Max	Mean	SD	p value
Male	64 (58.2)	9	132	60.8	39.8	
Female	46 (41.8)	7	132	61.3	44.1	0.947 (NS)
Total	110 (100.0)	7	132	61.0	41.5	
n = number; min = minimum, max = maximum; SD standard deviation						

Table-1: Age (months) and gender distribution of the studied subjects

Group	Diagnosis	N	%
Group I	GTCS	18	16.4
	SPS	6	5.5
	CPS	6	5.5
	Total	30	27.4
Group II	Febrile convulsion	30	27.4
Group III	BHS	9	8.2
	Syncope	12	10.9
	Pseudoseizure	4	3.6
	Total	25	22.7
Group IV	Control	25	22.7
GTCS = Generalized tonic clonic seizure; SPS = Simple partial seizure; CPS = Complex partial seizure; BHS = Breath holding spell			

Table-2: Diagnosis in the studied subjects

	min	max	Mean	SD	SE	LSD	p value
Group I	8.0	40.5	25.5	10.0	1.8	a	0.000
Group II	2.3	22.5	9.4	5.5	1.0	b	0.000
Group III	1.5	15.5	7.8	3.8	0.8	c	0.000
Group IV	2.0	20.0	7.4	5.2	1.0	d	0.390
Total	1.5	40.5	13.0	10.2	1.0	e	0.293
						f	0.854
						g	0.000

a = internal group comparison between Group I and Group II.; SD = Standard deviation
b = internal group comparison between Group I and Group III, SE = Standard error; c = internal group comparison between Group I and Group IV; LSD = Least significant; d = internal group comparison between Group II and Group III. Difference; e = internal group comparison between Group II and Group IV; f = internal group comparison between Group III and Group IV; g = internal group comparison between all groups

Table-3: Serum prolactin level (ng/ml) of first sample in the studied subjects

Serum Prolactin Level (ng/ml)	Diagnosis	Min	max	Mean	SD	p value
1st Sample	CPS	8.9	39.4	23.5	10.5	
	GTCS	8.0	40.5	29.2	9.0	
	SPS	8.2	24.6	16.3	6.4	0.015(Sig)
2nd Sample	CPS	1.5	14.9	8.3	4.7	
	GTCS	1.6	22.4	7.8	5.3	
	SPS	2.0	7.2	5.7	2.0	0.592(NS)

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

Table-4: Serum prolactin level (ng/ml) in the Group I subjects as per final diagnosis

Diagnosis	Abnormal		Normal		p value
	N	%	N	%	
Control	0	0.0	25	100.0	
BHS	0	0.0	9	100.0	
Febrile convulsion	0	0.0	30	100.0	
Pseudoseizure	0	0.0	4	100.0	
Syncope	0	0.0	12	100.0	0.000 (Sig)
CPS	4	66.7	2	33.3	
GTCS	15	83.3	3	16.7	
SPS	1	16.7	5	83.3	

GTCS = Generalized tonic clonic seizure, SPS = Simple partial seizure, CPS = Complex partial seizure,BHS =Breath-holding spell n = number

Table-5: Serum prolactin level (ng/ml) first sample across diagnosis in the studied subjects

	min	max	Mean	SD	SE	LSD	p value
Group I	10	20	16.8	4.0	0.7	A	0.083
Group II	6	40	20.0	8.3	1.5	b	0.006
Group III	10	35	22.2	8.2	1.6	c	0.261
Group IV							
Total	6	40	19.5	7.3	0.8	g	0.021

SD = Standard deviation; SE = Standard error; LSD = Least significant difference; mm = minimum; max = maximum; a is comparison between Group I and II; b is comparison between Group I and III; c is comparison between Group l and III; g overall comparison

Table-6: Time of collection of first blood sample from event (minutes) in the studied subjects

In Group I mean prolactin level of first sample was 25.5±10.0 SD. For second sample mean prolactin level was 7.5±4.7 SD (p = 0.000 significant). So the serum prolactin level of first sample was significantly raised than second sample in Group I.

Within group I the mean prolactin values for first sample were significantly higher in generalized tonic clonic seizure (40.5ng/ml) and complex partial seizure (39.4ng/ml) as compared to simple partial seizure (24.6ng/ml). The minimum level of prolactin of first sample for generalized tonic clonic seizure, complex partial seizure and simple partial seizure was 8.0 ng/ml, 8.9ng/ml and 8.2ng/ml. The mean prolactin level of first blood sample for generalized tonic clonic seizure was 29.2±9 SD, complex partial seizure was 23.5±10.5 SD, and for simple partial seizure was 16.3±6.4 SD (p value 0.015 which is significant). Maximum prolactin level of second blood sample for generalized tonic clonic seizure, complex partial seizure and simple partial

seizure was 22.4ng/ml, 14.9ng/ml, 7.2ng/ml. Mean prolactin level for generalized tonic clonic seizure, complex partial seizure and simple partial seizure was 7.8±5.3, 8.3±4.7 and 5.7±2.0 (p = 0.592 NS).

Our study showed that 83.3% (15) generalized tonic clonic seizure, 66.7% (4) complex seizures and 16.7% (1) simple partial seizure had elevated prolactin level. The sensitivity of elevated serum prolactin level for generalized tonic clonic seizure being 83.3% which is higher as compared to 66.7% sensitivity in complex partial seizure and 16.7% sensitivity in simple partial seizure (p value = 0.000 significant).

The mean time for collection of first blood sample from event (minutes) in the Group I, II, III was 16.8 minutes, 20 minutes, 22 minutes respectively (p value 0.083 = not significant).

In Group I, II, III with raised proalctin level 20 patients (30.3%) sample was taken at a duration < 20 minutes from the event. While out of those with normal prolactin level, 46 (69.7%) blood samples were taken at < 20 minutes from event (p value 0.006 significant). So peak prolactin level is attained if blood sample is taken within 20 minutes of event and begins to dip down beyond 20 minutes. In generalized tonic clonic seizure, 11(61.1%) had abnormal EEG while as 7 (38.9%) had normal EEG. In complex partial seizure 5 (83.3%) had abnormal EEG and in simple partial seizure 5 (83.3%) had abnormal EEG (p = 0.429 not significant). So 61.1% of generalized tonic clonic seizure, 83.3% of complex partial seizure and 83.3% of simple partial seizure had abnormal EEG study.

=In Group I with abnormal EEG the maximum prolactin level achieved was 40.5ng/ml and mean prolactin level was 27.0±8.8 SD for first blood sample. The prolactin level of first blood sample in Group I with normal EEG had a maximum level of 40.3ng/ml with a mean level of 21.9+12.3 SD. Second blood sample of patients with abnormal EEG had a maximum level of 22.4ng/ml with a mean of 8.1+4.9 SD. Those with normal EEG had maximum prolactin level of 14.9ng/rnl with a mean of 5.9±3.8 SD (p value = 0.208 and p value = 0.244 non-significant).

In generalized tonic clonic seizure 11 patients had abnormal EEG and out of them 11(100%) had abnormal prolactin. Five patients of complex partial seizure had abnormal EEG and out of them prolactin level was abnormal in 4(80%). One patient of simple partial seizure had abnormal prolactiñ level out of 5 (20%) patients with abnormal EEG (p = 0.002 signficant). So pick up rate of serum prolactin and EEG is same for generalized tonic clonic seizure cases. For complex partial seizure serum prolactin has almost similar pick up rate as EEG. In simple partial seizure EEG has better pick up rate than serum prolactin estimation.

The sensitivity and specificity of elevated prolactin for, epileptic seizures is 66.7% and 100% respectively. Positive predictive value is 66.7%, negative predictive value is 88.9 and accuracy of test is 90.9%. The mean time of collection of second blood sample in group I was 106.7+_6.7 from seizure event lying within range of 2hrs.

DISCUSSION

Epilepsy is the commonest neurological condition of the childhood.[6] A few disorders mimic epileptic seizures, especially complex partial seizures. We are often witness to 'seizures that do not look like seizures'. The most common imitators of seizures include syncope, cerebrovascular disorders, migraine, sleep and movement disorders, endocrine dysfunction, delirium, hyperventilation, dizziness, and vertigo.[7] Acute changes in the pituitary hormone levels, which occur following some of the seizures can help in differentiating epileptic seizure from pseudoseizure and febrile seizure. The most predictable post ictal changes are increased serum cortisol levels and serum prolactin levels. Because of the normal diurnal variation in serum cortisol levels and the relative delay in the post ictal elevations of serum cortisol, serum prolactin level is more useful as diagnostic measure of epileptic seizure.[6] This study was done to study role of post-ictal serum prolactin in diagnosis of seizures, differentiation from pseudoseizures and correlation with EEG as as diagonostic tool for seizure diagnosis.

Among 110 patients registered in our study, there were 64(58.2%) males and 46(41.8%) females with mean age of 60.8 and 61.3 months respectively. The serum prolactin level was highest in group I with mean level of 25.5ng/ml ±10 SD(p value =0.00) similar to findings of Banerjee S et al[2], Macooie et al[8] and Singhi et al.[9] The mean for first and second sample was 25.5ng/ml ±10 SD and 7.5ng/ml ±4.7 SD(p value =0.00) respectively. Within group I, mean serum prolactin levels(first sample) in generalized tonic clonic, complex partial seizures and simple partial seizure were 29.2±9SD,23.5±10.5SD and 16.3±6.4SD respectively (p value =0.015).The sensitivity of elevated serum prolactin levels in generalized tonic clonic, complex partial seizures and simple partial seizure was 83.3%(15/18), 66.7%(4/6) and 16.7% (1/5) respectively (P value =0.00).In our study none of patient with pseudoseizure in group III had elevated serum prolactin levels similar to results of Yerby MS et al.[10]

Among the patients in group I,II,and III; in whom serum sample for prolactin analysis was taken in less than 20 minutes from ictal state, 30.3%(20/66) had raised prolactin levels and 69.7%(46/66) had normal levels while as none 0/19(0.00%) had raised serum prolactin levels in group in whom sample was taken after 20 minutes (p value =0.006) consistent with findings of Banerjee S et al[2] and Wroe SJ et al.[11]

EEG was abnormal in 70% in group I. Among patients with generalized tonic clonic seizures all(100%) patients with abnormal EEG (11) had abnormal prolactin levels (11),4 patients out of 5(83.3%) with complex partial seizures had raised prolactin levels while as only one out of 5 (20%) with simple partial seizures had raised prolactin levels (p value =0.002) indicating a direct correlation of serum prolactin levels with EEG particularly in generalized tonic clonic and complex partial seizures similar to Mahendrappa et al.[3]

CONCLUSION

The utility of serum prolactin estimation is limited to

augmenting diagnosis of epileptic seizures. Although it cannot be used for differentiating various subtypes of epileptic seizures, yet it can easily be applied in cases of diagnostic uncertainly between true epileptic and pseudoepileptic events, before submitting our poor patients to more sophisticated and expensive investigations. Serum prolactin level were significantly high only in epileptic seizures and normal in conditions mimicking seizures.

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 09-05-2019; **Accepted:** 11-06-2019; **Published:** 30-06-2019