Serum Prolactin and Creatine Kinase Levels in Epileptic and Non-Epileptic Seizures

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Abstract:

The adverse effects of anticonvulsant drugs, duration and expense of therapy and social implications, make it essential for accurate diagnosis before starting treatment.

Many patients being treated as epileptics are not actually so. Moreover the coexistence of pseudoseizures with epilepsy is high. There is no single exposure, biochemical marker to differentiate between epileptic and non epileptic seizures (NES).

Ninety children were studied. They were subgrouped into 4 groups. Group I included 30 children with recent epileptic fits, aged 2-12 years. Group II consisted of 15 children with recent typical febrile seizures, aged 1-4.75 years. Group III involved 15 children with recent non-epileptic seizures, aged 5.2-12.7 years. Thirty clinically healthy children aged 3-12 years represented group IV (control group). Thorough history and clinical examination confirmed diagnosis and established exclusion criteria. CT brain, EEG and EMG imaging studies were done for all patients. Peripheral white blood cell count (WBCs), serum creatine kinase (CK) and prolactin levels were measured within lapse time (15-120 minutes) and 24 hrs post-ictally for all patients and once for control children. Post-ictal symptoms were present in more than 2/3 of epileptic seizures and 20% only of non-epileptic fits. WBCs and serum prolactin levels showed a transient early; while serum CK levels had a late post-ictal significant increase after generalized epileptic fits and to a much lower extent following focal and non-epileptic fits. The generalized tonic-clonic seizures (GTCS) showed higher elevation than other types of generalized epileptic fits. The three parameters showed a positive correlation with duration of seizures and a negative correlation with lapse time. Peripheral WBCs and serum prolactin returned to near normal levels one day post-ictally, while serum CK started to show a significant increase only 24 hrs after seizures. Serum prolactin levels were elevated more than twice and serum CK levels increased by more than 20 U/L in a high percentage of epileptic GTC seizures.

Conclusion: *The integrated interpretation of post-ictal symptoms, early assessment of peripheral WBCs and serum prolactin (<2 hrs) and late measurement of serum CK levels (>24 hrs) can compensate for our clinical uncertainty between epileptic and non-epileptic seizures before having to resort to more sophisticated and expensive investigations.*

Introduction:

Seizures may occur in as many as 1% of children. Identification of the seizure etiology helps identify potential treatment alternatives and the prognosis for the child.[1] NES occur in 20% of those referred for epileptic work up.[2] The coexistence of pseudoseizures with epilepsy is as high as 33%. Even 24-hr video monitoring, ambulatory EEG, provocative EEG test and SPECT may be inconclusive.[3] It is generally believed that generalized epileptic seizures may induce leukocytosis.[4] Post-ictal leukocytosis may be due to margination of WBCs.[5] Creatine plays a key role in cellular energy metabolism and is found at high concentration in metabolically active cells as skeletal muscle and neurons.[6] However, the discriminative power of CK in non-epileptic seizures was alleged to be limited.[7]

There is also a controversy as regards the usefulness of post-ictal serum prolactin levels in differentiating non-epileptic from epileptic seizures.[4,7] There is still no single biochemical marker for epileptic seizures.[3] Wide discrepancy remains the main feature of related study designs.

The present study aimed to determine the early and late post-ictal responses of serum prolactin, serum creatine kinase and peripheral WBCs, and to correlate with clinical findings in order to assess their relative importance in the diagnostic work up of a convulsing child.

Subjects and Methods:

Ninety children were included in this study. They were classified into 4 groups:

Group I (Epileptic Seizures): Thirty epileptic children (17 males and 13 females) with a recent epileptic

seizure (15-120 minutes), aged 2-12 years. Their seizures were classified according to the ILAE.

Group II (Febrile Seizures): Consisted of 15 children (9 males and 6 females) with a recent febrile seizure (typical clinical criteria and CSF examination when indicated)[8] within 15-120 minutes, aged 1-4.75 years.

Group III (Non-Epileptic Seizures): Included 15 children (5 males and 10 females) aged 5.2-12.7 years, presenting with a recent (15-120 minutes) non-epileptic seizures [7 breath holding attacks (BHA), 3 night terrors (NT), 3 pseudoseizures (PS) and 2 syncopal attacks].

All patients of the 3 studied groups were selected from the outpatient clinics of pediatric neurology, Menoufiya University Hospitals.

Group IV (control children): Thirty clinically healthy children (14 males and 16 females), aged 3-12 years, well matched for sex and socioeconomic status, presenting for reasons other than fever or seizures, represented control group. Informed written consents were taken from the guardians of patients and control children. Our exclusion criteria were any metabolic disturbances, central nervous system infections and diseases, muscular and endocrinal disorders, medications and brief seizures lasting <10 seconds. All patients and control children were subjected to the following:

- An elaborate history and thorough clinical and neurological examination with accurate description of seizures (type, duration, lapse time from onset till blood sampling and post-ictal symptoms).
- Imaging studies for patients only: EEG (using Galileo Sirius EEG, EB Neuro SPA, Italy) and CT brain (using Picker CT-Q2000, USA) and EMG (using NeuroPack Nihon EMG) to establish diagnosis and exclude other neurological and muscle diseases.
- Laboratory studies:[9]
  - Acute phase reactants (ESR, CRP and serum ferritin) to confirm exclusion criteria.
  - Peripheral WBCs count.
  - Serum levels of creatine kinase (CK) by ultraviolet spectrophotometry using creatine kinase NAC, Activated Human, Germany.
  - Serum prolactin concentrations were measured by electrochemi-luminescence immunoassay using Elyc Sys 1010 immunoanalyzer and its kits- Roche Diagnostics- Germany.

Serum levels of CK and prolactin were measured twice for all patients; shortly after fits (lapse time from 15-120 minutes) and 24 hrs later; difference of CK (24 hrs level - early post-ictal level) and ratio of prolactin (early post-ictal level/24 hrs level) were calculated. Serum levels of CK and prolactin were assessed once only for control children.

Statistical Analysis:

SPSS version 10[10] was utilized to analyze data in descriptive measures and statistical tests (Chi square, t-test, F-test, Pearson's and Spearman's correlations).

Results & Discussion:

The results are presented in tables I-VIII.

Table I: Demographic and clinical data of all studied children

Variables		Group I (Epileptic seizures) n= 30	Group II (Febrile seizures) n= 15	Group III (Non-epileptic seizures) n= 15	Group IV (Control children) n= 30
Age (years):	Range	2-12	1-4.75	5.2-12.7	3-12
	Mean±SD	6.08±4.15	2.8±1.3	7.9±3.97	6.5±4.95
Sex:	Males	17	9	5	14
	Females	13	6	10	16
Lapse time (min):	15-30	7	5	2	
	31-60	10	8	6	-
	61-90	7	2	3	
	91-120	6	0	4	
Seizure type:					
	GTC	14 (46.67%)	GTC: 15 (100%)	BHA: 7 (46.67%	-
	GT	9 (30%)		NT: 3 (20.0%)	
	Focal	7 (23.33%)		PS: 3 (20%)	
				Syncope: 2 (13.3%)	
Seizure Duration: (min)	<2	16	13	4	-
	>2	14	2	11	
Post-ictal symptoms*					
	+ve	19 (63.33%)	7 (46.66%)	3 (20%)	
	-ve	11 (36.66%)	8 (53.33%)	12 (80%)	-

**= Mostly fatigue and headache.*

Table II: Laboratory data of all studied children

Variables		Group I (n= 30)	Group II (n= 15)	Group III (n= 15)	Group IV (n= 30)	P-values
WBCs *(x10³)*	Mean ±SD	14.2 ±6.9	17.2± 7.4	7.15 ±3.2	6.9± 2.95	0.373
CK *(U/L)* : - Post-ictal:	Mean ±SD	77 ±39.87	87±61.54	79 ±22.09	*Random Mean ±S.D.*	0.824
- After 24 hrs:	Mean ±SD	190.5±140.11	219.5±124.82	84±11.5	76.75±32.62	0.003*
- Difference:	Mean ±SD	43±28.47	72.5±56.43	5.9 ±12.95	-	0.040*
Prolactin *(ng/ml)*						
- Post-ictal:	Mean ±SD	35.73±23.82	18.8±11.5	12.10±4.43	-	0.000**
- After 24 hrs:	Mean ±SD	11.7± 6.4	10.3±4.59	10±3.53	*Random X±S.D.*	0.600
- Ratio:	Mean ±SD	2.28±1.51	1.35±0.41	1.33±0.52	9.6±3.9	0.003*
					-	

**= Significant, **= Highly significant*

Table III: Laboratory data among epileptic patients with GTC seizures in comparison to other types of epileptic seizures

Variables			Epileptic patients with GTCS (n= 14)	Epileptic patients with other types of seizures (n= 16)	P-values
WBCs *(x10³)*		Mean±SD	16.81 ±9.67	7.3 ±3.05	0.125
Serum CK *(U/L):*	- Post-ictal:	Mean±SD	87.5±32.05	72.5 ±37.01	0.38
	- After 24 hrs:	Mean±SD	223.93±173.34	86.25±49.78	0.005*
	- Difference:	Mean±SD	76.43±64.58	23.75 ±22.29	0.002*
Serum Prolactin *(ng/ml):*	- Post-ictal:	Mean±SD	45.18±26.40	27.47±18.36	0.04*
	- After 24 hrs:	Mean±SD	15.96± 6.39	11.47±6.64	0.837
	- Ratio:	Mean±SD	2.91±1.90	1.74±0.78	0.031*

**= Significant*

Table IV: Laboratory data among epileptic patients with focal seizures in comparison to generalized epileptic seizures

Variables			Epileptic patients with focal seizures (n= 7)	Epileptic patients with generalized epileptic seizures (n= 23)	P-values
WBCs *(x10³)*		Mean±SD	7.81 ±2.14	15.74 ±11.51	0.545
Serum CK *(U/L):*	- Post-ictal:	Mean±SD	77.85±51.63	86.52 ±39.8	0.379
	- After 24 hrs:	Mean±SD	104.29±63.47	194.57±104.57	0.028*
	- Difference:	Mean±SD	23.65±26.42	52.23 ±28.04	0.040*
Serum Prolactin *(ng/ml):*	- Post-ictal:	Mean±SD	13.21±6.78	42.59±22.92	0.000*
	- After 24 hrs:	Mean±SD	12.14±5.98	11.78±6.25	0.105
	- Ratio:	Mean±SD	1.19±0.31	2.62±1.58	0.000**

** = significant, **= Highly significant*

Table V: Frequency of elevated levels of WBCs, serum CK and prolactin among all studied children

Variables	Group I (n= 30)	Group II (n= 15)	Group III (n= 15)	Group IV (n= 30)
Leukocytosis GTC	5 (35.71%)	9 (60%)	1 (6.67%)	0 (0%)
Other	2 (12.5%)			
CK (U/L)				
- Post-ictal:		4 (26.67%)	0 (0%)	
GTC	3 (21.43%)			
Other	0 (0%)			
- After 24 hrs:		6 (40%)	0 (0%)	0 (0%)
GTC	6 (42.86%)			
Focal	1 (14.29%)			
Other	1 (6.25%)			
- Difference:		11 (73.33%)	1 (6.67%)	
GTC	12 (85.71%)			
Other	4 (25.00%)			
Prolactin *(ng/ml)*				
- Post-ictal:		3 (20%)	1 (6.67%)	
GTC	10 (71.43%)			
Focal	8 (50%)			
Others	1 (14.29%)			
- After 24 hrs:		1 (6.67%)	0 (0%)	1 (3.33%)
GTC	3 (21.43%)			
Focal	1 (14.29%)			
Others	4 (25%)			
- Ratio:		2 (13.33%)	1 (6.67%)	
GTC	7 (50%)			
Focal	0 (0%)			
Others	4 (25%)			

Table VI: Correlation coefficients (P value) of laboratory data among epileptic children of group I

Variables	Serum CK			Serum Prolactin			Seizure type	Seizure duration	Lapse time
	Post-ictal	After 24 hrs.	Difference	Post-ictal	After 24 hrs.	Ratio			
Peripheral WBCs	0.825	0.973	0.647	0.587	0.892	0.586	0.021*	0.477	0.001*
Serum CK									
- Post-ictal	-	0.000**	0.002*	0.05*	0.533	0.325	0.081	0.002*	0.876
- After 24 hrs.	0.000**	-	0.000**	0.02*	0043*	0.189	0.01*	0.000**	0.658
- Difference	0.002*	0.000**	-	0.022*	0.011*	0.126	0.002*	0.01*	0.328
Serum Prolactin									
- Post-ictal	0.05*	0.02*	0.022*	-	0.000**	0.003*	0.018*	0.05*	0.01*
- After 24 hrs.	0.533	0.189	0.126	0.04*	-	0.406	0.696	0.903	0.328
- Ratio	0.325	0.043*	0.011*	0.000**	0.012*	-	0.027*	0.01*	0.05*

*= *Significant*, **= *Highly significant*

Table VII: Correlation coefficients (P value) of clinical and laboratory data of epileptic patients with GTC seizures (Group I)

Variables	Serum CK			Serum Prolactin			Seizure duration	Lapse time
	Post-ictal	After 24 hrs.	Difference	Post-ictal	After 24 hrs.	Ratio		
Peripheral WBCs	0.586	0.566	0.673	0.979	0.889	0.97	0.05*	0.008*
Serum CK								
- Post-ictal	-	0.00**	0.072	0.214	0.505	0.592	0.092	0.085
- After 24 hrs.	0.000**	-	0.002*	0.085	0.559	0.316	0.002*	0.023*
- Difference	0.072	0.002*	-	0.04*	0.837	0.102	0.000**	0.012*
Serum Prolactin								
- Post-ictal	0.214	0.085	0.04*	-	0.184	0.000**	0.002*	0.000**
- After 24 hrs.	0.505	0.559	0.837	0.184	-	0.692	0.504	0.174
- Ratio	0.592	0.316	0.102	0.000**	0.692	-	0.000**	0.000**

*= *Significant*, **= *Highly significant*

Table VIII: Correlation coefficients (P value) of laboratory data of group II (Febrile seizures)

Variables	Serum CK			Serum Prolactin			Seizure duration	Lapse time
	Post-ictal	After 24 hrs.	Difference	Post-ictal	After 24 hrs.	Ratio		
Peripheral WBCs	0.597	0.873	0.205	0.943	0.902	0.84	0.754	0.353
Serum CK								
- Post-ictal	-	0.000**	0.267	0.733	0.937	0.457	0.917	0.190
- After 24 hrs.	0.000**	-	0.015*	0.668	0.826	0.469	0.674	0.732
- Difference	0.267	0.015*	-	0.695	0.534	0.695	0.593	0.243
Serum Prolactin								
- Post-ictal	0.733	0.668	0.695	-	0.003*	0.001*	0.917	0.446
- After 24 hrs.	0.937	0.826	0.534	0.003*	-	0.143	0.764	0.323
- Ratio	0.457	0.469	0.695	0.001*	0.143	-	0.754	0.913

*= *Significant*, **= *Highly significant*

Children with febrile seizures (group II) were significantly younger than other studied children (P<0.05). Males were more predominant among epileptic children of groups I and II; while females were more affected by non-epileptic seizures (group III), in agreement with literatures.[11]

GTC, GT and focal seizures were found respectively in 46.67, 30% and 23.33% of epileptic children as previously reported by El-Khayat et al.,[12] Abd El-Khalik et al.,[13] Zaferiou et al.,[14] and Senbil et al.[15] The predominance of generalized seizures among epileptic children was attributed either to a genetic predisposition or to a quick secondary bilateral synchronization.

The duration of non-epileptic seizures among children of group III was markedly prolonged comparable to the duration of epileptic and febrile seizures in accordance with Shah AK et al, who showed that non-epileptic seizures had a much longer mean seizure duration than did epileptic seizures.[4]

In the current study, about 2/3 of epileptic children experienced post-ictal symptoms mostly in the form of headache and fatigue, in comparison to 20% only of children with non-epileptic seizures. Ettinger et al.[16] previously reported that all epilepsy patients had at least one post-ictal symptom, while more than 50% of non-epileptic patients had none.[16]

As regards the laboratory data; the present work showed that although the mean WBCs didn't differ significantly in between the 4 studied groups; however, a higher percentage of epileptic children had leukocytosis (35.71%) after GTCS in comparison to other types of epileptic seizures (12.5%) and non-epileptic seizures (6.67%).

McCarthy and Dale[17] said that WBCs increase after rigorous muscle contractions, so it was hypothesized

that elevation of WBCs after a seizure is a result of muscular activity.[4] In fact; among all studied variables; the WBCs were found to be significantly correlated with seizure types, being markedly higher among those with GTCS accompanied with vigorous muscle contractions and with negative correlation with lapse time (i.e. transient leukocytosis).

The present study showed that mean serum levels of CK did not significantly change early post-ictally (within 2 hours); with high levels (>200 U/L) in 21.43% of GTC epileptic seizures and 26.67% of febrile seizures in comparison to none of other types of epileptic and non-epileptic seizures. Serum early post-ictal CK levels were positively correlated to seizure duration of epileptic children (table VI). Libman et al.[18] previously reported that serum CK is highly specific for diagnosing generalized seizures with improved sensitivity by sampling serum at least 3 hrs post-ictally.[18] Chesson et al.[19] revealed that post-ictal elevation of serum CK appears to be related to the intensity of muscular activity.[19]

Neufeld et al.[20] reported elevation of serum CK early post-GTCS in a nearly equal figure to ours (25%). On the other hand, Willert et al.[7] attributed a limited diagnostic power to serum CK (between epileptic and non-epileptic seizure).

The study of late (24 hrs post-ictally) serum levels of CK showed that GTC seizures led to their marked increase above 200 U/L in about 50% of epileptic children with GTC seizures, while only 6.25% of other types of epileptic seizures were accompanied by such an increase. An elevation by (>20 U/L) within one day post-ictally was found in 85.71% of those who suffered GTC seizures, in comparison to 25% of all other epileptic seizure types. It should be noted that the increment within 24 hr post-ictally was marked (i.e. >20 U/L) regardless of normal serum levels in the early and late post-ictal states in a high percentage of patients with GTC seizures.

Therefore the magnitude of elevation of serum CK is a more sensitive indicator of GTC epileptic seizures than its absolute level and that this elevation occurs late post-ictally.

The late post-ictal absolute serum levels of CK and also their magnitude of increment during one day from seizures were positively correlated with the duration of the epileptic seizures (table VI), in agreement with Glotzner,[21] who said that the maximum value of CK activity was found late post-ictally; similarly Neufeld et al.[20] concluded that a high increase of CK levels occurs in the second day in GTC seizures, even when sequential tests are within the normal range; they added that an increase of at least 15 U/L is highly indicative of an epileptic event.[20]

As regards the serum prolactin; the current study showed that its mean post-ictal levels are markedly elevated early after epileptic seizures, with significantly higher elevations following GTC seizures (in 71.43%) than other generalized epileptic seizures. Focal epileptic seizures caused such an elevation in only 14.29%, of cases in near figures to those found after febrile seizures (20%) and still higher than figures in non-epileptic seizures. The early increased post-ictal levels were positively correlated with seizure duration but negatively correlated to lapse time. This indicates that generalized epileptic seizures, especially so GTC seizures result in a marked early increase of serum prolactin with more increase following prolonged seizures, but it is transient, decreasing by time. Thereafter, serum prolactin levels became significantly higher than control only in 21.43% late post-ictally following GTC seizures. The ratio of serum prolactin early post-ictally to late post-ictally was more than double after 50% of GTC seizures and in 25% of other epileptic seizures; however focal seizures didn't result in such a markedly high ratio after any of focal events. Febrile seizures and non-epileptic seizures caused this doubling of serum prolactin level early post-ictally when compared to their late post-ictal levels (as representatives of their basal level) in very low percentages (13.39% and 6.67% respectively). Many researchers found an early elevation of serum prolactin after generalized epileptic seizures, more marked following GTC; with blunting of this increase soon, to the degree that their levels one day post-ictally returned to their basal values.[3,22] An increase to more than twice was found by Shah et al.,[4] in about 50% of generalized seizures while only 2% of non-epileptic seizures showed such an increase. However; their absolute values of serum prolactin were above the upper limit of normal in 86% of generalized seizures and in 5% of non-epileptic seizures.[4] As an explanation for the immediate post-ictal increase of serum prolactin level especially after GTC seizures; Banerjee et al.[3] said that in GTCS, there is a presumed spread of electrical activity from the ventromedial hypothalamus, leading to release of a specific prolactin regulator into the hypophyseal portal system, while in typical febrile seizures, sub-clinical electrical activity doesn't exist since the after discharges are less intense and transient to project to the ventromedial hypothalamus, whereas non-epileptic seizures completely lack electrical discharges.[3,23-25]

In the present study, the ratio of early post-ictal serum levels of prolactin to basal levels (regained 24 hrs post-ictally) was found to be positively correlated with seizure duration but negatively correlated to lapse time, indicating the transient nature of this elevation. Individual variations in the current study showed that the positivity of post-ictal symptoms, the significant early rise

of WBCs and serum prolactin levels, the late increase of serum CK levels and high ratios of serum prolactin did not occur post-ictally in the same epileptic events; however, there was only some overlap. So, statistical significance can be maximized and a reliable diagnostic score can be formulated through the judicious use of a combination of these variables. It is to be concluded that early peripheral WBCs and absolute levels of serum prolactin (within 2 hrs) and late serum CK (after one day) along with the ratio of early post-ictal to basal (late post-ictal) serum levels of prolactin can be assessed in cases of diagnostic uncertainty between epileptic and non-epileptic seizures. A Scoring System might prove through wide-scale prospective studies to be accurate and reliable in the diagnostic work up of a convulsing child.

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