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Usefulness of Serum NT-proBNP in Diagnosis of Generalized Seizures in Egyptian Children

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Abstract

Background

Seizures may occur in as many as 1% of children. The most urgent type of seizures is generalized tonic-clonic seizures (GTCS). N-terminal prohormone of brain natriuretic peptide (NT-proBNP) has been considered as a promising biomarker in numerous acute illnesses. We aimed to evaluate usefulness of NT-proBNP for diagnosis of generalized seizures in children.

Materials and Methods

This prospective case control study was conducted upon 80 children who were classified into four groups; Group I: included 20 patients with idiopathic generalized epileptic seizures. Group II: included 20 patients with focal epileptic seizures. Group III: included 20 patients with febrile seizures. Group IV: included 20 apparently healthy, age and sex matched children as a normal control. Complete blood count (CBC), blood chemistries, including random blood glucose, calcium, sodium, C-reactive protein (CRP) level, serum prolactin and NT-proBNP were performed for all children.

Results

Our results revealed significant increase of both prolactin and NT-proBNP in generalized epileptic and febrile seizure groups than in focal epileptic and control groups ($p< 001$). The ROC curve analysis showed NT-proBNP, at a cut-off value of > 384 pg/ml, sensitivity (90 %), and specificity (70.2%) which was near the results of prolactin at a cut-off value> 25.9 ng/ml, and showed sensitivity (95.1%), and specificity (71.3%).

Conclusion

Based on the results, NT-proBNP increase in generalized seizures either epileptic or febrile; and may be a promising marker to adjust the diagnosis of it at the emergency setting, when history and clinical presentation are equivocal.

Key Words: Children, N-terminal prohormone of brain natriuretic peptide, Prolactin, Seizures.

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1- INTRODUCTION

Seizures are considered one of the most dangerous neurological emergencies in pediatrics and cause about 1% of all emergency room (ER) visits (1), most of them are febrile seizures and generalized epilepsy (2). The most urgent and dramatic type of seizures are generalized tonic-clonic seizures (GTCS). The majority of GTCS are benign but some lead to complications such as cardiac arrhythmias, fractures, rhabdomyolysis, aspiration pneumonia, acute kidney injury and behavioral complications such as delirium or psychosis (3). There is still no single investigation to confirm the diagnosis of epileptic seizures (4). There is some controversy as regards the use of serum prolactin levels in differentiating non-epileptic from epileptic seizures (5).

Prolactin is a hormone secreted from the anterior pituitary gland and inhibited by tubero-infundibular dopamine neurons in the arcuate nucleus of the hypothalamus. Post-ictal serum prolactin may be elevated after paroxysmal epileptic events and, despite the uncertainty surrounding its diagnostic accuracy, it has been proposed as an adjunct to post-facto diagnosis when history of seizures is equivocal (6). Pro-hormone brain-type natriuretic peptide (BNP) is a 108-amino-acid (AA), which was first isolated from porcine brains in 1988 (7, 8). BNP is considered as a cardiac neuro-hormone, which is secreted from ventricular myocytes by increased intraventricular pressure (9).

When BNP has been secreted, it splits into a biologically active 32-aa BNP and inactive 76-aa NT-proBNP (10, 11). Volume or pressure load of the heart leads to increased BNP synthesis and secretion (12). Clinical applications of increased BNP include a promising biomarker of congestive heart failure reflecting the cardiac function (11, 12). Several studies demonstrated that BNP is a risk marker in patients with HIV infection (13), severe sepsis (10), acute Kawasaki disease (14), and acute Puumala Hantavirus infection (15), hand foot mouth disease investigation showed that high levels of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) are associated with the risk of cardiopulmonary failure (16). This study aimed to compare NT-proBNP versus prolactin for diagnosis of generalized seizures in Egyptian children.

2- MATERIALS AND METHODS

2-1. Study design and population

This is a prospective case control study that included 80 patients collected from Pediatric Emergency Room, Children's University Hospital, Minia University, Egypt. They were randomly selected during the period from July 2019 to January 2020. Our children were divided to:

Group I (generalized epilepsy), included 20 patients with generalized epileptic seizures. Children diagnosed as idiopathic generalized epilepsy presenting with a convulsive episode not triggered by infection.

Group II (focal epilepsy), included 20 patients with focal epileptic seizures. Diagnosis and classification of epilepsy was done according to ILAE classification of epilepsies, 2017 (17).

Group III (febrile seizures), included 20 patients with febrile seizures. Children with febrile seizures were children for whom parents or caregivers reported a convulsive event associated with elevated body temperature (>38 °C) without a previous history of afebrile seizures (18). Children with doubtful diagnostic features of FS were excluded.

Diagnosis was confirmed by our pediatric neurology staff members based on recurrent seizures and EEG changes and according to ILAE classification of epilepsies (2017).

Group IV: included 20 apparently healthy children serving as normal control, age and sex matched to the diseased groups without history of any neurological disorders.

2-2. Inclusion and exclusion criteria

Inclusion subjects were children aged from 6 months to 12 years; seizures group presented within 2 hours postictal. We excluded patients with any metabolic disturbance, developmental, structural or neurological abnormalities, infective central nervous pathology, sepsis and septic shock, patients on drugs known to alter prolactin or NT-proBNP level (like phenothizine, haloperidol, metoclopramide, opiates, imipramines, fluoxetine, and cimetidine).

2-3. Laboratory measurements

The studied groups were subjected to full history taking, thorough clinical examination and laboratory investigations including: complete blood count (CBC), blood chemistries, including random blood glucose, calcium, sodium, C-reactive protein (CRP) level, serum prolactin using the Immune spec Prolactin ELISA (Enzyme-Linked Immunosorbent Assay) kit, and NT-proBNP level concentrations in serum were determined using the ELISA kit supplied by EIAab (Wuhan EIAab Science Co. Ltd, Wuhan, China).

Five ml of venous blood was withdrawn from cubital vein into appropriately labeled tubes after complete aseptic technique. Two ml of them were collected in tubes containing EDTA as anticoagulant for CBC, and three ml was collected in tubes, left to clot for 30 minutes then the sera were separated from the cells using centrifuge at 3000 RPM for 15 minutes; and stored at -20 °C until blood chemistry, serum prolactin and NT-proBNP assay was done. Blood samples were collected within two hours of the event in all seizures groups and the exact interval between the event and collection of blood was noted (Elapsed time). Cut-off point for prolactin and NT-proBNP was determined according to ROC curve, the point with maximum specificity and sensitivity.

2-4. Ethical consideration

The ethical committee of Faculty of Medicine, Minia University, Egypt, approved our study (No 241:6/2019). Informed written consents were obtained from the patient's parents before enrollment in our study.

2-5. Statistical methods

Data were statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 21.0. Descriptive statistics were expressed for quantitative data by mean, standard deviation and range, while they were presented for categorical data as number and percentage. Analyses were done for quantitative data among the three groups using One Way ANOVA test followed by Post-hoc Tukey correction between each two groups. However, analyses were done for qualitative data using Chi-square test or Fisher Exact test. The degree of relationship between the variables was calculated using Pearson correlation analysis. Receiver operating characteristic (ROC) curve analysis was performed using SPSS to determine the optimal cut-off values and the diagnostic performance of the variable. The diagnostic sensitivity and specificity were studied using ROC curves. The level of significance was taken at (P-value < 0.05).

3- RESULTS

Our study was conducted upon 80 children (51 males and 29 females) who were classified into four groups; Group I: included 20 patients with generalized epileptic seizures (14 males and 6 females) with mean age 2.3 ± 0.5 years. Group II: included 20 children with focal epileptic seizure (13 males and 7 females) with

mean age 2.2 ± 0.5 years, Group III: included 20 children with febrile seizures (12 males and 8 females) with mean age 2.0 ± 0.4 years. Group IV: included 20 apparently healthy, age and sex matched children as a normal control (**Table.1**). **Table.1** also showed statistically significant longer duration of event in epileptic groups than febrile seizure group ($p < 0.01$).

Table-1: Clinical characteristics of studied groups

Variables	Groups				P- value
	Group (I) Generalized Epilepsy (n=20)	Group (II) Focal Epilepsy (n=20)	Group (III) Febrile seizure (n=20)	Group (IV) Control (n=20)	
Age (year)	2.3 ± 0.5	2.2 ± 0.5	2.0 ± 0.4	2.2 ± 0.4	0.26
Gender (M/F)	14/6	13/7	12/8	12/8	0.72
Weight (kg)	11.5 ± 1.3	11.3 ± 1.8	11.4 ± 1.0	11.8 ± 1.4	0.66
Duration of seizure (min)	10.1^{b} ± 2.1	12.2^{a}±1.7	4.9^{c} ± 1.4	-	**< 0.01**

In addition, our results showed significant higher total leukocytic count (TLC), and C-reactive protein (CRP) levels in febrile seizure, and generalized epileptic groups than the focal epileptic and control groups ($p<0.01$). Also, significant higher NT-proBNP and prolactin levels in febrile seizure group and generalized epileptic group than in focal epileptic seizure group and control group ($p < 0.01$,each of them) (**Table.2**).

Table-2: Laboratory data of studied groups.

Variables	Groups				P- value
	Group (I) Generalized Epilepsy (n=20)	Group (II) Focal Epilepsy (n=20)	Group (III) Febrile seizure (n=20)	Group (IV) Control (n=20)	
Hb (g/dL)	11.22 ± 0.79	10.9 ± 0.90	11.31 ± 1.1	11.44 ± 0.97	0.46
TLC (*10^3/mm)	13.93^{a} ± 1.12	7.18^{b} ± 1.08	13.65^{a} ± 1.21	6.59^{b} ± 1.41	< 0.01
RBG (mg/dL)	77.6 ± 6.2	79.8 ± 5.6	78.4 ± 8.9	81.4 ± 6.5	0.32^{NS}
CRP (mg/L)	15.32^{a} ± 3.15	2.88^{b} ± 2.83	14.05^{a} ± 3.82	1.79^{c} ± 0.86	< 0.01
Na (mg/dL)	137.7 ± 10.5	138.9 ± 11.6	138.3 ± 8.1	139.0 ± 11.2	0.98
Ca (mg/dL)	10.17 ± 1.25	9.80 ± 0.88	10.01 ± 1.33	10.53 ± 1.29	0.26
Prolactin (ng/ml)	39.4^{a} ± 9.74	15.3^{b} ± 2.83	32.2^{a} ± 8.30	14.60^{b} ± 3.03	< 0.01
NT-proBNP (pg/ml)	616^{a} ± 134.9	184.9^{b} ± 48.1	537.8^{a} ± 123.8	168.7^{b} ± 36.2	< 0.01

Abbreviations: Hb= blood hemoglobin, TLC=total leucocyte count, RBG=random blood glucose, Na=corrected sodium, Ca=serum calcium, NT-proBNP= N-terminal prohormone of brain natriuretic peptide.

Table.3 showed inverse significant negative associations between the time elapsed since the episode of seizure and both serum prolactin and NT-proBNP (r=0.61 and 0.54, respectively, p<.001), **Table.3**. Besides, significant positive correlation between serum prolactin and NT-proBNP (r=0.65, p< 0.01). The ROC curve analysis showed NT-proBNP at a cut-off value of >384 pg/ml showed sensitivity (90%), and specificity (70.2%), which was near the results of prolactin at a cut-off value > 25.9 ng/ml which showed sensitivity (95.1%), and specificity (71.3%) (**Table.4, Figure.1**).

Table-3: Correlations between serum prolactin, and NT-proBNP and some studied parameters.

Variables	Serum Prolactin		Serum NT-proBNP	
	(r)	P- value	(r)	P- value
Age	-0.06	0.65 NS	0.06	0.67
Body weight	0.17	0.19 NS	0.18	0.24
Temp. at presentation	0.09	0.57 NS	0.09	0.85
Time elapsed	-0.61	< 0.01**	-0.54	< 0.01
Prolactin	-	-	0.65	< 0.01

Abbreviations: NT-proBNP= N-terminal prohormone of brain natriuretic peptide.

Table-4: ROC curve analysis between serum prolactin, and NT-proBNP for prediction of generalized seizures.

Parameters	AUC	Cutoff	Sensitivity (%)	Specificity (%)
Prolactin	0.903	> 25.9 (ng/ml)	95.1	71.3
NT-proBNP	0.788	> 384 (pg/ml)	95.2	69.1

Abbreviations: NT-proBNP= N-terminal prohormone of brain natriuretic peptide.

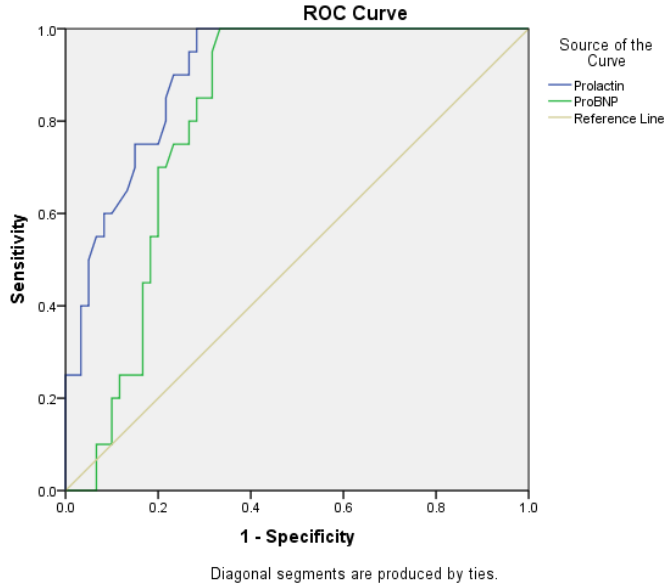

Fig.1: ROC curve analysis between serum prolactin and NT-proBNP for prediction of generalized seizures.

4- DISCUSSION

We aimed to compare NT-proBNP versus prolactin for diagnosis of generalized seizures in Egyptian children. Our results showed significant higher TLC and CRP levels in febrile seizure, and generalized epileptic groups than focal epileptic and control groups. This was in agreement with Biyani et al. (19) who found that TLC increase after vigorous muscle contractions, so the elevation of TLC after a seizure may be a result of muscular activity or nor-epinephrine release due to stress during epileptic seizures. Also, Abdel Salam et al. (20), studied serum levels of CRP, Interleukin-6 (IL-6) in children with febrile seizures. They found that CRP and TLC levels were significantly higher in febrile patients in relation to control children, and these findings highlight the association between high levels of inflammatory markers and development of fever as a body response to underlying infection. Similarly, they supported the hypothesis that the cytokine network is activated and could have a role in the pathogenesis of febrile seizures.

The diagnosis of epilepsy based on clinical manifestations, or routine laboratory investigations is not usually an easy decision. The wide clinical presentations of different types of convulsions increase the difficulties in diagnosis. Because the urgency and course of treatment are quite different depending on the diagnosis, rapid and accurate diagnosis may be essential. So finding a rapid diagnostic test for convulsion may be useful in ER. When studying NT-proBNP levels in our patients we found significant higher levels in their febrile seizure and generalized epileptic groups than in focal epileptic and control groups with insignificant difference between febrile seizure and generalized epileptic group. Our results were in accordance with Rauchenzauner et al. (21), who showed plasma concentration of NT-proBNP was significantly higher 4 hours postictal compared to 24–48 h postictal ($p< 0.001$). They showed increased NT-proBNP levels in children with tonic–clonic seizures and febrile convulsions compared to children with partial motor seizures, syncope, or controls. High levels of NT-proBNP in children with generalized fits may be explained by two mechanisms. First, increased NT-proBNP secretion from cardiac myocytes, secondary to an increase in stress and noradrenaline release during epileptic fits (21), which may occur secondary to increased blood pressure, and heart rate changes that occur during epileptic fit (22).

Although prolonged tachycardia may lead to relative ischemia of the myocardium, tachycardia may not be the only underlying factor for the elevation of NT-proBNP levels (21). Second, mechanism for increased NT-proBNP levels may be its secretion from the brain through the hypothalamus and catecholamine triggers, endothelin, and arginine vasopressin (23) mediate their production. NT-proBNP is considered a part of the central mechanism for control of blood volume (24). Also, high concentrations of NT-proBNP may be associated with the cerebral ischemia during generalized seizures (25), suggesting that NT-proBNP secretion is produced by brain tissue ischemia, reflecting increased biosynthesis and secretion from ischemic brain tissue, especially from the hypothalamus (26).

In addition, experimental findings in paralyzed rats showed that serum BNP levels increased three-fold after 30-min of generalized seizures (27). The two mentioned mechanisms of increased NT-proBNP can also explain the insignificant difference between focal epilepsy and control group. Lower cardiac or brain effect to trigger NT-proBNP secretion may explain these stable levels of NT-proBNP in focal seizures. Our results were in contrast with the result obtained by Nass et al. (3), who studied complete NT-proBNP

measurements from baseline to 24 hours of 28 patients with no changes over time (p= 0.28), except in 2 patients who had a peak at 6 hours with levels above 250 pg/mL. As regards serum prolactin in our study, we found significant higher levels in their febrile seizure and generalized epileptic groups than in focal epileptic and control groups with insignificant difference between febrile seizure and generalized epileptic group. Many researchers (5, 28-30) such as Chaurasiya et al. in 2013 (5) showed an early increase of serum prolactin after generalized seizures was more marked following generalized tonic clonic convulsions with returning to its basal levels 24 hours postictally. Increase of serum prolactin levels may be explained by abnormal electrical discharge passing through the hypothalamus that may disrupt the normal functioning.

In addition, generalized neuronal discharge during seizure activity stimulates the hypothalamus either directly through specific neurotransmitter changes (GABA and dopaminergic system) or through the release of other substances, and so, increase serum prolactin level during generalized seizures (5). In agreement with our results, a study done by Stöcklin et al. (31) found that, serum prolactin increased in children with febrile seizures compared to controls, but no differences were detected between children with febrile and epileptic seizures.

On the other hand, another study done by Macooie et al. (32) contradicts our result, as they found that febrile seizures were not associated with increased serum prolactin level and stated that increased prolactin level within 2 hours may be suggestive of epileptic origin of the seizure and they explained that the subclinical electrical activity in febrile seizures is too brief to affect the ventromedial hypothalamus or lead to a rise in prolactin level. In current study, results showed that there was significant correlation between both serum NT-proBNP and prolactin levels and time elapsed since the episode of seizures. This was in agreement with Chaurasiya et al. (5), who stated that, the maximum elevation of prolactin was seen within 15 to 30 minutes postictally and it became normal after two hours of post-ictal period. Finally, the ROC curve analysis of both serum NT-proBNP and prolactin for prediction of generalized seizures in our children showed nearly the same sensitivity and specificity. Fisher (33) studied the serum prolactin in diagnosis of epileptic seizure and showed 100% sensitivity for tonic-clonic seizures and 84.4% sensitivity for complex partial seizures. Overall, elevated prolactin occurred in 84% of patients with epileptic events and 28.8% of patients with non-epileptic events. Finally, we recommended:

1. Serum NT-proBNP and prolactin have high diagnostic accuracy in febrile and generalized epileptic seizures and may be a helpful marker for accurately diagnosing postictal states in the emergency setting.
2. Further studies, large and wide scale study on a large population with febrile seizures to find statistically differences among the simple and complex febrile seizures groups with NT-proBNP.
3. Further study to compare epileptic and pseudoseizures for the use of NT-proBNP to differentiate between them.

5- CONCLUSION

Our findings showed increase of NT-proBNP and prolactin levels in children with febrile and generalized epileptic seizures, which may be used to adjust the diagnosis of generalized seizures at the emergency setting, when history and clinical presentation are equivocal.

6- AUTHOR CONTRIBUTIONS

Both authors equally contributed. They read and approved the final manuscript.

7- CONFLICT OF INTEREST: None.

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