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ORIGINAL ARTICLE

Diagnostic Value of High Mobility Group Box-1 (HMGB1) in Children with Refractory Epilepsy

Mohamed Elsayed Amer [1], Esraa Elsayed Mohamed Al [1], Hossam Mostafa Kamal [1], Doaa Metwaly AbdElmonem [2*]

[1] Pediatrics Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt

[2] Clinical Pathology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt

Corresponding Author:
Esraa Elsayed Mohamed
Email:
dresraa42020@gmail.com

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ABSTRACT

Background: Epilepsy is a neurological disorder with features of unpredictable epileptic seizures that are periodic and recurrent, caused by variance in inhibitory and excitatory pathways in the central nervous system (CNS).The aim of this study was to investigate the diagnostic value of HMGB1 in children with refractory epilepsy.

Method: This case-control study included 42 children with refractory epilepsy who attended the pediatrics neurology unit and pediatric outpatient clinic at Zagazig University Hospitals to investigate the diagnostic value of HMGB1 in children with refractory epilepsy and another healthy children group, who were in the same age range as the patient group, included as a control group.

Results: There was a statistically significant higher HMGB1 concentration among our cases than controls. The cut-off point of HMGB1 concentration was >7ng/ml. HMGB1 concentrations had high sensitivity (80.95%), specificity (69.05%), predictive positive value (72.3%), negative predictive value (78.4%) and accuracy (75%).

Conclusions: Refractory epilepsy among children remains a great concern and a massive challenge worldwide; despite advances in diagnostics and treatment, refractory epilepsy is still a major medical problem with high morbidity and mortality. Therefore, novel biomarkers for early detection of refractory epilepsy should be used, for example, HMGB1 as a potential biomarker for early detection of refractory epilepsy.

Key words: Refractory epilepsy, HMGB1, RAGE, TLR4, AEDs.

INTRODUCTION

A Change in the electrical activity of the brain caused by a variety of circumstances characterizes epilepsy, a frequent neurological condition. It encompasses numerous seizure types with varying degrees of severity, seizure semiology, origin, outcomes, and therapy. Since it is a chronic condition, antiepileptic medications must be used in long-term therapy (AEDs) [1].

Refractory epilepsy is characterized by the occurrence of uncontrolled seizures despite the administration of two antiepileptic medications (AEDs) in combination or as monotherapies that have been well-tolerated and selected adequately. Refractory epilepsy is characterized by frequent adjustments to AEDs during the course of the disease. Patients with uncontrolled seizures were identified using patterns of AED prescription modifications [2].

Consequences for patients, their families, and society include enduring neurobehavioral and neuropsychiatric issues and further brain damage as a result of frequent and severe epileptic seizures [3].

Numerous inflammatory compounds and humoral mediators, such as matrix metalloproteinases (MMP) cytokines, and high mobility group box-1, can contribute to epileptogenesis (HMGB1) [4].

HMGB1 is a nuclear non-histone protein that is widely expressed in practically all cell types. High mobility group box-1 (HMGB1) is crucial for DNA repair in nuclei, modulation of transcription activity, and chromatin structure preservation. However, HMGB1 is regarded as a characteristic damage-associated molecular pattern (DAMP) due to its extracellular translocation and its release from a variety of brain cells, including neurons and glia, which contributes to the pathogenesis of numerous CNS illnesses [5,6].

The expression and translocation of HMGB1 may also be induced by the hyperexcitability. Antiepileptic medication therapy may focus on inhibiting HMGB1 and the signaling pathways that it activates. Reviewing the HMGB1-related pathway's alterations in epileptic brains and its impact on the control of neuronal excitability and epileptic seizures is shown here [7]. The present study aimed to perform diagnosis of refractory epilepsy in relation to the presence of High Mobility Group Box-1 in the plasma of the patients.

METHODS

Study Design:

This case-control study has been performed at the pediatrics neurology unit, pediatric outpatient clinic, and clinical pathology department in Zagazig University Hospitals from January 2021 to September 2021. Written informed consent was obtained from all participants' parents, the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (IRB#:9075 Approval date: 7-11-2021) for studies involving humans. The study was done on 42 children with refractory epilepsy and 42 healthy children as a control group with the following inclusion and exclusion criteria.

Inclusion Criteria:

All cases with the following features were included: approval to participate in the study.; children with refractory epilepsy aged between 1 year and 16 years; both genders; healthy children as a control group of the same age between 1 and 16 years old. All patients were recruited from the pediatric department of Zagazig University hospitals and outpatient clinics.

Exclusion Criteria:

Refusal to participate in the study. Children with refractory epilepsy younger than 1 year old or older than 16 years old. Children with accompanied diseases in another system. Children with mental retardation or suffering from any neurological diseases other than epilepsy were excluded from the study.

All patients were subjected to the following: Complete history taking, full clinical examination, and laboratory routine investigations. Samples were collected from patients as follows: 1.5 ml on EDTA tube for CBC and 2 ml on plain tubes for liver functions, CRP, and electrolytes assay. A complete blood count was performed on an automated cell counter (XN330 Sysmex, Japan) with differential count on Leishmania-Giemsa stained peripheral. Electrolytes (Na, K, Ca, CL, Mg), were estimated on Sensa core ST200 plus. Liver function tests, blood urea, and creatinine were done on Cobas8000.

Specimens' collection and storage:

For the purpose of isolating the serum, three ml of venous blood were drawn from each subject's vein and collected under strict aseptic conditions. The blood was then placed in a sterile clean separator tube and allowed to coagulate. To extract the serum, centrifugation was carried out for 20 minutes at a speed of 2000–3000 rpm. The serum was then collected and placed in an Eppendorf tube, where it was kept at -40 C until the research day. If precipitation was visible, the sample was centrifuged one more.

Measurement of HMGB1:

HMGB1 was measured in serum samples by ELISA using the manufacturer's procedure. Kits were provided by Sun Red biotechnology company (China) Catalogue No. 201-12-1636 named Human High mobility group protein B1 (HMGB-1) ELISA Kit.

Data Analysis:

The IBM SPSS software program version 23.0 was used. The range (minimum and maximum), mean, standard deviation, median, and interquartile range were used to characterize quantitative data (IQR). In order to determine the significance of the acquired results, a 5-percent threshold was used. It was a Chi-square test used to find associations between groups and other variables. Student t-test: to calculate the quantities of data of normal distribution and to compare between two studied groups. Receiver-operating characteristic (ROC) curve analysis was used. As a result, the p-value was insignificant: $P > 0.05$, $P \leqslant 0.05$ as significant, and $P < 0.01$ as highly significant.

RESULTS

Regarding the demographic data and family history, there was no statistically significant difference in age, weight, and sex between the case and control groups, while the consanguinity was statistically significant (Table 1).

The current findings, regarding past history, showed that the average number of hospitalization times was 9.26 ± 5.9 with an average duration of epilepsy of 41.1 ± 31.9 months. Generalized tonic-clonic was the commonest type of the first fit among the case group (54.8%). 26.2% had once status epilepticus in addition 38.1% & 45.2% of the case had a previous loss of consciousness and febrile convulsion respectively. Stress was the most common risk factor (19.0%), while the present history data showed that daily frequency was the highest (40.5%), 42.9% of cases had three lines of treatment (The most common line), and the average hospital duration was 8.9 ± 6.1 days (Table 2).

Generalized epileptic activity was the most common EEG finding (23.8%), while 11.9) of the case group had brain atrophy by MRI (Table 3).

Our results concerning CBC and electrolytes table showed that there was a statistically significantly higher RBC count and Hb level among control than cases while Mg was statistically significantly higher among cases than control. Otherwise, there was no statistical significance difference regarding WBCs, platelets count, Ca, Na, and K between the case and control groups. On the other side, for liver and kidney function tests, the current results showed that there was a statistically significant higher total protein level among control than cases while SGOT and SGPT were statistically significantly higher among cases than control. Otherwise, there was no statistically significance difference regarding other variables between the case and control groups. There was statistically significantly higher HMGB1 concentration among cases than controls (Table 4).

The cut-off point of HMGB1 concentration was >7 ng/ml. HMGB1 concentration had high sensitivity (80.95%), specificity (69.05%), predictive positive value (72.3%), negative predictive value (78.4%), and accuracy (75%) (Table 5).

Binary logistic regression showed that consanguinity and HMGB1 concentration above 7 ng/mL were significant independent predictors for refractory epilepsy (Table 6).

There was no statistically significant correlation between HMGB1 and age, disease duration, number of attacks in a month, and laboratory parameters in the studied refractory epilepsy group (Table 7).

Table 1: Comparison between case and control groups regarding socio-demographic characteristics and family history

Variables	*Case No= 42 (%) Mean ± SD Median (Range)*	*Control No=42 (%) Mean ±SD Median (Range)*	**Test**	**P-value**
Age(year)	7.8 ± 3.6 7 (3-16)	8.3 ± 3.3 7.7 (3-16)	M.W= 0.6	0.5
Weight (Kg)	21.9 ± 6.4 20.5 (5-43)	24.1 ± 6.5 23 (13-36)	T= 1.4	0.17
Sex *Male* *Female*	 18 (42.9%) 24 (57.1%)	 26 (61.9%) 16 (38.1%)	χ^2=3.1	0.07
Consanguinity *Yes* *No*	 28 (66.7%) 14 (33.3%)	 17 (40.5%) 25 (59.5%)	χ^2=5.8	**0.016***
Family history of epilepsy *Yes* *No*	 16 (38.1%) 26 (61.9%)	 10 (23.8%) 32 (76.2%)	χ^2=2.1	0.15

SD: Stander deviation, MW: Mann Whitney test, χ2: Chai square test, t: test of significant

Table 2: Clinical data (past and present history) among the case group

Variables	*Case No= 42 (%)*
Past history	
Risk factors • *No* • *Fever* • *Mobile phone* • *Sadness* • *Stress* • *Tiredness*	 17 (40.5%) 5 (11.9%) 2 (4.8%) 4 (9.5%) 8 (19.0%) 6 (16.3%)
Consciousness • *Loss* • *Not loss*	 16 (38.1%) 26 (61.9%)
Previous febrile convulsions • *No* • *Yes*	 23 (54.8%) 19 (45.2%)

Previous status epilepticus	
• *No*	12 (28.6%)
• *Once*	11 (26.2%)
• *Twice*	8 (19.0%)
• *Three times*	6 (14.3%)
• *Four times*	2 (4.8%)
• *Five times*	3 (7.1%)
Type of 1st fit	
• *Generalized tonic clonic*	23 (54.8%)
• *Focal arms*	4 (9.5%)
• *Focal eyes &arms*	3 (7.1%)
• *Focal eyes*	3 (7.1%)
• *Focal Lt side*	5 (11.9%)
• *Focal Rt side*	2 (4.8%)
• *Absence*	2 (4.8%)
Epilepsy duration (months)	
Mean ± SD	41.1 ± 31.9
Median	30
(Range)	(7-144)
Numbers of hospitalization Times	
Mean ± SD	
Median	9.26 ± 5.9
(Range)	7
	(2-29)
Present history	
Frequency	
Daily •	17 (40.5%)
1-5 times/week •	10 (23.8%)
< once /month •	4 (9.5%)
1-5 times /month •	11 (26.2%)
Treatment lines	
Two lines •	3 (7.1%)
Three lines •	18 (42.9%)
Four times •	10 (23.8%)
Five times •	11 (26.2%)
Hospital duration (days)	
Mean ± SD	8.9 ± 6.1
Median	7
(Range)	(1-29)

Table 3: Electroencephalogram (EEG) and Magnetic resonance imaging (MRI) findings among the case group

Variables	*Case No= 42 (%)*
Electroencephalogram (EEG) • Normal • Generalized epileptic activity • Epileptogenic focus • post ischemic changes • Others	 14 (33.3%) 10 (23.8%) 7 (16.7%) 7 (16.7%) 4 (9.5%)
Magnetic resonance imaging (MRI) • Normal • Brain atrophy • Agenesis • Hypoxic injury • Hydrocephaly • Cerebral palsy • Focal lesions • Encephalomalacia • Malformation • Rt Sub-Dural Hygroma	 21 (50%) 5 (11.9%) 3 (7.1%) 4 (9.5%) 2 (4.8%) 2 (4.8%) 2 (4.8%) 1 (2.4%) 1 (2.4%) 1 (2.4%)

Table 4: Comparison between case and control groups regarding the complete blood count (CBC), electrolytes, liver and kidney functions and HMGB1

Variables	*Case No= 42 (%)* *Mean ± SD* *Median* *(Range)*	*Control No=42 (%)* *Mean ± SD* *Median* *(Range)*	T-Test	P-value
RBCs (× 10^6/uL)	4.2 ± 0.5 4.1 (2.9-5.3)	4.4 ± 0.67 4.5 (3.1-5.5)	2.1	**0.04***
Hemoglobin (g/dl)	10.7 ± 1.9 11.1 (1-14.2)	13.2 ± 1.2 13.6 (10.2-14.6)	6.9	**0.001****
WBCs (× 10^3/uL)	10.6 ± 4.3 9.5 (4.2-23)	11.6 ± 3.2 11.1 (6.2-16.5)	1.2	0.2
Platelets(×10^3/uL)	371.9± 129.04 356 (126-854)	420.8 ± 403.6 361 (167-2863)	0.7	0.4
Serum Ca (mg /dl)	9.9 ± 0.7 9.9 (8.3-11.79)	10.3 ± 0.72 9.94 (8.9-11.6)	0.2	0.8
Serum Mg(mg /dl)	2.38± 0.59 2.29	1.96 ± 0.28 1.97	4.1	**0.001****

	(1.08-4.5)	(1.12-2.39)		
Serum Na (mmol /L)	138.5 ± 6.1 138 (128-155)	136.3 ± 19.02 139.5 (19-150)	0.4	0.5
Serum K(mmol /L)	4.7 ± 0.73 4.8 (2.7-6.2)	4.47 ± 0.77 4.41 (3.15-6.01)	1.7	0.09
Total bilirubin(mg/dl)	0.41 ± 0.39 0.3 (0.11-2.35)	0.53 ± 0.26 0.51 (0.12-1.01)	1.7	0.09
Total protein(g/dl)	6.28± 1.5 6.3 (3.15-9.5)	7.41 ± 0.66 7.25 (6.18-8.77)	4.4	**0.001****
Serum G.O.T(AST) (U/L)	30.2 ± 22.1 22.2 (9.1-96.7)	19.38 ± 16.04 16.4 (1.99-93.3)	2.6	**0.01***
Serum G.P.T(ALT) (U/L)	19.9 ± 15.7 14.4 (4-78.2)	13.37 ± 11.39 9.75 (1.5-55.4)	2.1	**0.03***
Creatinine(mg/dl)	0.3 ± 0.07 0.31 (0.19-0.53)	0.31 ± 0.09 0.33 (0.15-0.44)	0.26	0.8
Serum urea nitrogen(mg/dl)	11.6 ± 5.9 9.7 (1.09-32.8)	11.59 ± 4.7 11.2 (4-19.5)	0.1	0.9
HMGB1 Concentration(ng/mL)	9.61 ± 2.8 8.7 (7.5-11.9)	7.55 ± 2.4 6.4 (6-9.7)	M.W= 459	**<0.001****

*: Significant (P<0.05), **: Highly significant (p<0.001), IQR=inter-quartile range, M.W= Mann-Witenny test.

Table 5: The cut-off point of HMGB1 concentration and diagnostic ability of HMGB1 concentration to discriminate refractory epilepsy from healthy controls

HMGB1	**Cut off point**	**AUC**	**P**	**95% CI**	
Concentration	>7 ng/*ml*	0.74	**<0.001****	0.66-0.91	
	Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**
	80.95%	69.05%	72.3%	78.4%	75%

**highly statistically significant different

Table 6: Univariate binary logistic regression for the predictive factors for epilepsy among the studied group

HMGB1	**Odds ratio**	**P**	**95% CI**
Consanguinity	2.94	**0.017***	(1.21-7.16)

Family history of Epilepsy	2.7	0.25	(0.49-14.79)
concentration >7 ng/ml	9.48	**<0.001****	(3.45-26.04)

Table 7: Correlation between HMGB1 and other parameters in studied refractory epilepsy group (n=42)

	HMGB1	
	R	P
Age(year)	-0.064	0.688
Epilepsy duration (months)	0.094	0.553
Frequency	-0.207	0.189
Treatment lines	0.038	0.812
RBCs ($x10^6$/uL)	0.224	0.153
WBCs ($x10^3$/uL)	-0.034	0.829
Hemoglobin (g/dl)	0.098	0.536
Platelets ($x10^3$/uL)	-0.153	0.333
Serum Ca (mg /dl)	0.122	0.443
Serum Mg (mg /dl)	0.202	0.199
Serum Na (mmol /L)	0.233	0.138
Serum K (mmol /L)	0.107	0.499
Serum G.O.T (U/L)	-0.177	0.261
Serum G.P.T (U/L)	0.025	0.875
Creatinine (mg/dl)	0.163	0.303
Serum urea nitrogen (mg/dl)	-0.288	0.064
C-reactive protein (mg/L)	-0.113	0.477

DISCUSSION

Epilepsy is a neurological disorder with features of unpredictable epileptic seizures that are periodic and recurrent, caused by variance in inhibitory and excitatory pathways in the central nervous system (CNS). 50–70 million individuals worldwide suffer from epilepsy, which now accounts for 0.75% of the world's health burden [8].

Consequences for patients, their families, and society include enduring neurobehavioral and neuropsychiatric issues and further brain damage as a result of frequent and severe epileptic seizures [9].

Our study was a case-control study that included 42 children with refractory epilepsy, who attended the pediatrics neurology unit and pediatric outpatient clinic at Zagazig University Hospitals to investigate the diagnostic value of HMGB1 in children with refractory epilepsy, and 42 healthy children, who are at the same range of age with the patient group, was included as a control group.

Regarding the socio-demographic characteristics among our subjects, there was no statistically remarkable variation in age, weight, and sex between the case and control groups. Also, there was no statistically significant variance regarding family history between the case and control groups, while the consanguinity was statistically significant.

The average number of hospitalization times between our cases was 9.26 ± 5.9 with an average duration 41.1 ± 31.9 months of epilepsy and generalized tonic-clonic was the most common type of 1st fits among the case group (54.8%). 26.2% had once status epilepticus, 38.1% and 45.2% of the cases had previous loss of concentration and febrile convulsion respectively.

Stress was the most common risk factor (19.0%). Daily frequency was the highest (40.5%), 42.9% of cases had three lines of treatment and the average hospital duration was 8.9 ± 6.1 days.

A similar case-control study by Salih was conducted on 150 subjects. Two important demographic characteristics that were linked to the occurrence of epilepsy were found in this investigation. Consanguinity, which is associated with family history of epilepsy, was the second factor. The first was a history of epilepsy in the family. When compared to a control group of healthy individuals, both factors were notably elevated in epileptic patients. In agreement with us, there was no statistically remarkable variation in age, weight, and sex between the case and control groups [4].

Kannoth and his team showed that having an epileptic family member increased the likelihood of developing both generalized and localization-related epilepsies [10].

Hunza and colleagues did not find a link between epilepsy and parental consanguinity in a group known to have high rates of this marriage practice even though 50% of cases had a family history of epilepsy. On the other hand, their results were in the same line as ours considering the time of the previous hospitalization, duration of epilepsy, or daily frequency [11]. Also, there is an agreement between us regarding the average number of hospitalization times, duration of epilepsy, or daily frequency [12].

Our findings revealed that generalized epileptiform abnormalities were the most common EEG finding (23.8%), while 11.9% of the case group had brain atrophy by MRI.

Four of the eight children in the Mohamed et al. series had clear epileptoterns of symptomatic generalized epilepsy; their seizures were marked by generalized tonic, myoclonic, and spasm symptoms, which were connected to generalized epileptiform abnormalities on EEG [13].

Our results cleared that there was statistically significantly higher total protein level, RBC count, and Hb level among control than cases. Also, Mg, SGOT, and SGPT were statistically significantly higher among cases than in control. Otherwise, there was no statistically significant difference regarding WBCs, platelets count, Ca, Na, and K between the case and control groups.

Contrary to our results, Suo et al. [14] analyzed several laboratory indices among patients with refractory epilepsy (RE) and reported that no marked changes in levels of hemoglobin, hematocrit, RBCs, WBCs, and platelets of 21 cases with refractory epilepsy. Furthermore, Kose et al. [15] did not observe thrombocytopenia in any case, however they revealed elevation in Na and K levels in patients with RE.

There was a statistically significantly higher HMGB1 concentration among our cases than controls. The cut-off point of HMGB1 concentration was >7ng/ml. HMGB1 concentrations had high sensitivity (80.95%), specificity (69.05%0, predictive positive value (72.3%), negative predictive value (78.4%), and accuracy (75%). Binary logistic regression showed that consanguinity and HMGB1 concentration above 7 ng/mL were significant independent predictors for refractory epilepsy. There was no statistically significant association between HMGB1 and age, disease duration, number of attacks in a month, and laboratory parameters in the studied refractory epilepsy group.

Choi et al. [16], reported that serum levels of HMGB1 were found to be considerably higher in patients with febrile seizures (9.0ng/mL in afebrile controls, 24.8ng/mL in febrile controls, and 30.1ng/mL in a patient with afebrile status epilepticus who was resistant to AEDS).

Walker et al. [17] found a similar increase in the total HMGB1 serum concentration following seizures in epilepsy patients who had been seizure-free for more than six months (8.6 3.5 against 1.25 0.71, p 0.0001) and in those who were resistant to AED treatment (8.6 3.5 versus 0.7 0.3, p 0.002). In contrast, the Salih study found no statistically significant variation in serum HMGB1 levels between epilepsy patients who were controlled and those who were refractory to treatment [4].

The non-significant results in some studies can be explained by a number of assumptions. First off, the time of the HMGB1 measurement can have a big impact on the outcome. In the kainic acid-induced model, HMGB1 was upregulated in the hippocampus, peaking 2 times at 3 h and 6 days following kainic acid administration. At 12 hours after kainic acid, there was a considerable buildup of HMGB1, which may have been caused by the release of HMGB1 as a result of the neuronal death caused by kainic acid [18].

In a different study, Fu et al. [19] used a kainic acid-induced epilepsy model. They found that the HMGB1 level in the control group was higher than in the epileptic group after 24 hours and rose at 72 hours (p 0.05). The majority of these data are consistent with the idea that during an acute epileptic condition, HMGB1 is translocated and released in the brain.

Therefore, timing HMGB1 measurements outside of a specific window of time following a seizure may not accurately reflect HMGB1 concentration in epileptic individuals. Second, there are several HMGB1 isoforms (nonacetylated, acetylated, reduced, disulfide, and oxidized). Furthermore, each isoform has a unique expression and activity [20].

For instance, Ravizza et al. [21] demonstrated that disulfide HMGB1 is expressed early in newly diagnosed epileptic cases and that its persistence is linked to later seizures. In contrast, chronic, drug-resistant epilepsy has persistent expression of acetylated, disulfide HMGB1 isoforms. The ELISA method, which assays total HMGB1 irrespective of isoforms, is well established. As a result, a high concentration of one isoform combined with the absence of another can produce inaccurate results regarding the total amount of HMGB1.

The central nervous system's neuronal, glial, and endothelial cells as well as circulating leukocytes are all separate sources of HMGB1 production. There was no correlation between the HMGB1 produced by circulating leukocytes and that produced as a result of brain injury [3].

CONCLUSION

We concluded that refractory epilepsy among children remains a great concern and a massive challenge worldwide. High Mobility Group Box-1 (HMGB1) has a significant diagnostic value for refractory epilepsy. Further studies must be done to analyze the potential role of HMGB1 in the diagnosis of childhood refractory epilepsy and it is mandatory to pay attention to this fact while outlining the recent guidelines in the management of children with RE.

Declaration of interest

The authors report no conflicts of interest. The authors along are responsible for the content and writing of the paper.

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