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Original article

Assessment of Interleukin-1β in Children with Intractable Epilepsy

Hana R. Omar [a], Elham A.Nawar [a], Neveen T. Abed [a],
Walid A. Abdelhalim [b], Sahar F. Farrag [a]

Abstract:

Background: In the central nervous system (CNS), an imbalance between excitatory and inhibitory pathways may lead to epileptic seizures. IL-1β has been shown to have a proconvulsive impact in animal models. Objectives: to measure interleukin 1 beta as an inflammatory biomarker in children with intractable epilepsy and to evaluate the diagnostic and prognostic value of this biomarker. **Patients and methods:** This comparative cross-sectional research was done on 60 children, 30 with intractable epilepsy and 30 with medically controlled epilepsy as the control group. All patients were subjected to careful history-taking, clinical examination, imaging, and laboratory investigation. **Results:** There were statistically significant differences between groups concerning family history of epilepsy, criteria of disease in the epileptic group (except type of seizures), anthropometric measurements, radiological assessment, and EEG in the studied groups, and the performance of IL-1β to detect patients with prolonged seizures. There were no statistically significant differences amongst groups concerning age, sex, or IL-1β in the studied groups, and there was no correlation between IL-1β and clinical data in the epileptic group (except for the duration of fits). **Conclusion:** The results of this research revealed no statistically significant variance amongst interactable epileptic patients and controlled epilepsy patients concerning IL-1β level. However, IL-1β could detect epileptic patients with prolonged seizures and there was a significant positive association between IL-1β and the duration of fits.

Keywords: interleukin-1β, intractable epilepsy, pediatrics.

[a] Pediatrics Department, Faculty of Medicine Benha University, Egypt.

[b] Clinical and Chemical Pathology Department, Faculty of Medicine Benha University, Egypt.

Corresponding to:
Dr. Sahar F. Farrag.
Pediatrics Department, Faculty of Medicine Benha University, Egypt.
Email: shrfraj458@gmail.com

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Introduction

Intellectual dysfunctions and attention deficiencies are only two of the behavioral and cognitive issues that have been linked to pediatric epilepsy, which is a chronic illness of the brain. According to the International League against Epilepsy (ILAE), a person with epilepsy is someone who experiences "two or more unprovoked seizure attacks occurring at least one day apart." [1]

The prevalence of epilepsy has increased to the point that it now accounts for 0.75 percent of the world's total health burden, impacting 50 to 70 million individuals worldwide. [2]

About a third of people who have epilepsy also suffer from drug-resistant epilepsy, which is defined as epilepsy that cannot be treated by a minimum of two antiepileptic drugs. Children who have drug-resistant forms of epilepsy may see a decline in their IQ over time. [3]

It is believed that frequent and severe epileptic seizures contribute to further brain damage and chronic neurobehavioral and neuropsychiatric problems, which have profound ramifications for cases, their families, and society as a whole**.** [4]

The cytokines known as IL-1 alpha (IL-1α), IL-1 beta (IL-1β), and IL-1 receptor antagonist (IL-1RA) are all members of the IL-1 cytokine family. All three of them bind the IL-1 receptor (IL-1R). The majority of IL-1β is found in the secretion, whereas the majority of IL-1α is found linked to membranes. [5]

This study aimed at measuring interleukin 1 beta as an inflammatory biomarker in children with intractable epilepsy and evaluating the diagnostic and prognostic value of this biomarker.

Subjects and methods

This comparative cross-sectional research was done on 60 children (30 with intractable epilepsy and 30 with medically controlled epilepsy as the control group). Subjects were recruited from the pediatric department of Benha University Hospital throughout the time that ranged from January 2022 to September 2022.

Inclusion criteria

Children who have epilepsy that can be controlled by medication and who have been diagnosed and categorized in accordance with the standards outlined in the 2017 International Classification of Epileptic Syndromes [6], both sexes, and age after 1 month until 18 years.

Exclusion criteria

Epileptic children who were admitted to the hospital for an infectious disease

Study groups

Intractable epilepsy group: included 30 with intractable epilepsy and controlled epilepsy group: included 30 with medically controlled epilepsy.

Ethical considerations

The study was carried out after approval from the Ethical Research Committee of the Faculty of Medicine of Benha University and informed parental written consent from all parents of subjects involved in the study (IRB) {M.S.14.9.2020}.

The Methods

Careful history taking (including personal history, complaint and history of present disease, and family history), clinical examination (general examination and system examination), imaging (electroencephalography (EEG), CT brain, and magnetic resonance imaging (MRI), and laboratory investigation (complete blood count, C-reactive protein, and interleukin (IL)-1β).

Sampling

Venipuncture was performed using a sterile needle and a single-use plastic syringe to collect two milliliters of blood from each participant.

Complete blood count, Using a Sysmex 21-kx cell counter, the following parameters were evaluated: red blood cell count; hemoglobin level; hematocrit value; platelet count; and white blood cell (WBC) count.

C-reactive protein (CRP): CRP was detected qualitatively using CRP-Latex

Slide Agglutination, which was given by SpinReact, Spain.

Human interleukin (IL)-1β measurement: Using a commercial kit intended for research purposes (Catalog No. IL-1B-435Hu.23T), a double-antibody sandwich ELISA (Enzyme Linked Immune Sorbent Assay) was carried out in order to determine the concentration of human IL-1β in the serum (company Biokit for scientific research).

Statistical analysis

The data were then processed using SPSS version 24 (Armonk, NY: IBM Corp) which required them to be coded, inputted, and processed on a computer. After tabular and diagrammatic representations of the results were created, they were then interpreted. The following are some examples of descriptive statistics: mean, standard deviation, range, frequency, and percentage.

Results

There were no statistically significant differences among groups concerning age or sex. However, the intractable epilepsy group had a statistically greater incidence of family history of epilepsy compared to the controlled epilepsy group. (Table 1)

The intractable epilepsy group had a statistically lower age of disease onset, a lower duration between fits and a higher duration of fits, a higher rate of status epilepticus, and a higher frequency of prolonged fits compared to the controlled epilepsy group. Also, most cases with intractable epilepsy had symptomatic epilepsy, compared to the controlled epilepsy group, in which most cases were idiopathic. In addition, all cases in the intractable epilepsy group had administered various drugs and antiepileptic drugs. (Table 2)

There was a statistically significant difference among the groups concerning radiological assessment and EEG. The intractable epilepsy group had a statistically higher frequency of abnormal MRI, CT, brain, and EEG. (Table 3)

Patients with intractable epilepsy had higher IL-1β compared with patients with controlled epilepsy. However, statistical analysis revealed no discernible differences among the groups. (Table 4)

There was a statistically significant positive association among IL-1β and duration of fits, while there were no statistically significant correlations among IL-1β and (age, age of disease onset, hemoglobin, WBCs, platelets, or C-reactive protein). (Table 5)

ROC analysis was conducted to evaluate the efficacy of IL-1β to detect patients with prolonged seizures; the AUC was 0.795 (95% confidence interval: 0.608–0.982), p=0.009. At a cutoff point $\geq$ 900 pg/ml, the sensitivity was 70% and the specificity was 80%. (Table 6)

Anthropometric measurements of the studied groups [Figure 1]

ROC curve of the performance of IL-1β to detect epilepsy patients with prolonged seizures [Figure 2]

Table 1: Socio-demographic data of the examined groups.

		Interactable epilepsy		Controlled epilepsy		Test	P value
		N=30	%	N=30	%		
Sex	**Male**	19	63.3%	17	56.7%	X^2=0.27	0.59
	Female	11	36.7%	13	43.3%		
Age (years)	**Median**	3		4		U=1.23	0.145
	Range	0.2-10		0.3 -11			
Family history of epilepsy	**No**	15	50.0%	24	80.0%	X^2=8.1	<0.001*
	Yes	15	50.0%	6	20.0%		

X^2; chi-square test, U: Mann-Whitney U-test

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Table 2: Criteria of disease in the epileptic group.

		Interactable epilepsy		Controlled epilepsy		Test	P value
		N=30	%	N=30	%		
Age of disease onset (months)	Median	4		18		U=3.2	0.018*
	Range	1 - 66		6 -72			
Duration of fits (minutes)	Median	22.5		10		U=4.3	0.009*
	Range	3 - > 60		2-15			
Type of seizures	Generalized Tonic Clonic	19	63.3%	15	50.0%	X^2=1.2	0.43
	Generalized Tonic	11	36.7%	15	50.0%		
History of prolonged seizures	Yes	20	66.7%	0	0.0%	X^2=20.1	<0.001*
	No	10	33.3%	30	100.0%		
Duration between fits (days)	Median	7		30		U=8.4	<0.001*
	Range	1-60		15-100			
Number of status epilepticus/year	Median	2		0		U=10.1	<0.001*
	Range	1-5		0			
Etiology	Idiopathic	4	13.3%	20	66.6%	X^2=18.5	<0.001*
	Symptomatic	18	60%	5	16.7%		
	Provoked	8	26.7%	5	16.7%		
Treatment	Phenoparbitone	0	0.0%	4	13.3%	X^2=23.5	<0.001*
	Valproate	0	0.0%	11	36.7%		
	Levetiracetam	0	0.0%	9	30.0%		
	Combination	30	100%	6	20.0%		

Table 3: Radiological assessment and EEG in the studied groups.

		Epilepsy group		Controlled epilepsy			
		N=30	%	N=30	%		
MRI	**Normal**	3	10.0%	24	80.0%	X^2=132.5	<0.001*
	Brain atrophy	5	16.7%	2	6.7%		
	Brain malacia	5	16.7%	2	6.7%		
	Dilated ventricles	4	13.3%	0	0.0%		
	Calcifications	4	13.3%	1	3.3%		
	Brain tumor	2	6.7%	0	0.0%		
	Partial agenesis of corpus collasum	2	6.7%	0	0.0%		
	Basal ganglia infraction	2	6.7%	0	0.0%		
	Mild occipital demyelination	3	10.0%	1	3.3%		
CT brain	**Normal**	8	26.7%	25	83.3%	X^2=122.3	<0.001*
	Cerebralatrophy	5	16.7%	2	6.7%		
	Ventricular dilatation	4	13.3%	0	0.0%		
	Encephalomalacia	3	10.0%	2	6.7%		
	Cerebral infraction	2	6.7%	0	0.0%		
	Ischemic Area	4	13.3%	0	0.0%		
	Calcification	4	13.3%	1	3.3%		
EEG	**Normal**	2	6.7%	21	70.0%	X^2= 54.9	<0.001*
	Abnormal	28	93.3%	9	30.0%		

X^2; chi-square test, MRI: magnetic resonance imaging, EEG: Electroencephalogram, CP: Cerebral palsy, HIE: Hypoxic ischemic encephalopathy, NF: Neurofibromatoses, TS: Tuberous sclerosis

Table 4: IL-1 β in the examined groups.

		Interactable epilepsy		Controlled epilepsy		Test	P value
		N=30	%	N=30	%		
IL-1 β (pg/ml)	**Mean±SD**	982.7±729		800.9±1042.1		U=2.77	0.053
	Median	915.7		733.9			
	Range	198-4394.8		393.5-3601			

U: Mann-Whitney U-test

Table 5: Correlation between IL-1 β and clinical data in the epileptic group.

	IL-1 β (pg/ml)	
	r	**P value**
Age/ years	0.151	0.424
Age of onset (years)	-0.114	0.459
Duration of fits (min.)	0.370	0.044*
Hemoglobin (gm/dl)	0.014	0.943
WBCs (l)	-0.187	0.322
Platelets (10^3/l)	-0.083	0.663
C-reactive protein (mg/dl)	-0.043	0.823

r: Correlation Coefficient, *: significant, WBCs: white blood cells

Table 6: Performance of IL-1 β to detect patients with prolonged seizures.

	AUC	95% CI		Cut-off value	Sensitivity	Specificity	P value
IL-1 β (pg/ml)	0.795	0.608	0.982	>900	70%	80%	0.009*

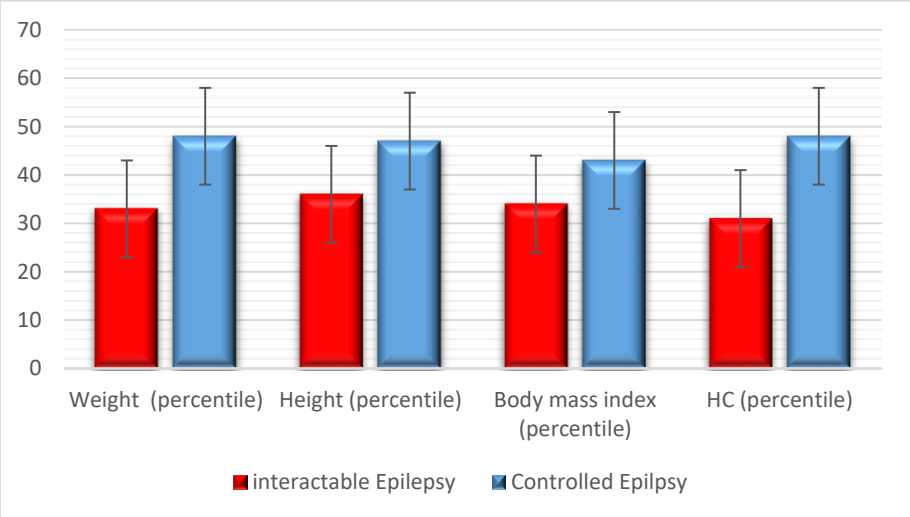

Figure 1: Anthropometric measurements of the studied groups.

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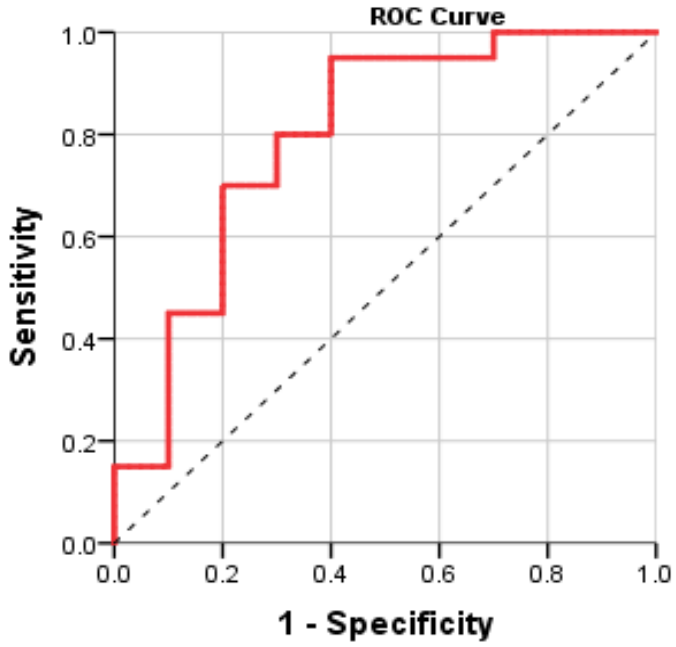

Figure 2: ROC curve of performance of IL-1 β to detect epilepsy patients with prolonged seizures.

Discussion

Epilepsy is a serious neurological disorder characterized by seizures that happen over and over again, without warning [7]. An imbalance between excitatory and inhibitory pathways in the brain has been linked to epilepsy.

In the present research, the interactable epilepsy group had a statistically greater incidence of family history of epilepsy (50%) compared to the controlled epilepsy group (20%), p = <0.001.

Our findings corroborated those who found that 29.8% of cases in the resistant group had a positive family history of seizure, compared with 22.3% of cases in the control group (p = 0.08) [8].

In the current study, criteria of disease in the epileptic group:

Our findings were consistent with those of who reported that symptomatic epilepsy was more common in the poorly managed group 19 (57.5 percent), compared to the controlled group 42 (53percent). The correlation between poorly managed epilepsy and the presence of symptoms was found to be statistically significant (P <0.001) [9],

Seventy-five (75.3) percent of children with refractory epilepsy recorded an age of under one year at seizure start, while only 43 percent of children with responsive epilepsy indicated an age of under one year at seizure onset. The odds ratio (OR) for children with refractory epilepsy having several seizure types is 9.5 times higher than it is for children with responsive epilepsy (6.5 percent vs. 36.5 percent) [10]. In addition, everyday seizures were recorded by 90 percent of children with refractory epilepsy, compared to 28 percent of children in the responsive group (OR=24.1). The prevalence of a history of status epilepticus and the existence of an epileptic syndrome were reported by 43 and 26.9 percent of children with refractory epilepsy, respectively [10].

In the present research, the intractable epilepsy group had significantly lower (non-significant difference) weight, height, BMI, and head circumference percentiles compared with the controlled epilepsy group. In addition, they had a statistically significant higher frequency of delayed

developmental milestones compared to controls.

According to the study which examined the nutritional status in children with refractory epilepsy, epileptic children have a lower mean body weight for age and gender than typically developing children of the same age and gender. Seven cases were malnourished, depending on how you define the term. One of the patients was overweight, but not too many. None of the patients saw a decrease in height [11]. We found similar outcomes.

In the present study, the intractable epilepsy group had a statistically higher frequency of abnormal MRI and CT brains.

In the same weight, it was found that out of 142 cases in whom CT scans were done, 102 (71.83%) had a normal CT scan, while 40 cases (28.17%) had an abnormal CT scan. Magnetic resonance imaging (MRI) was done in 118 cases, out of which 72 cases (61.02%) had normal MRI and 46 cases (39.98%) had abnormal MRI [12, 13].

In the current investigation, IL-1β was greater in individuals with intractable epilepsy than in cases with controlled epilepsy; statistical analysis revealed no discernible differences among the groups.

Both human investigations and animal experiments have shown that neuroinflammation is related to the development of epilepsy. According to the data, IL-1β and IL-1 receptor antagonists (IL-1RA) are of special importance. The neurotoxic and pro-convulsant features of IL-1β are countered by the neuroprotective and anticonvulsant actions of IL-1RA in animal models of epilepsy [14, 15].

Cases in the present research that had a history of intractable epilepsy also had a substantially greater IL-1β level than those who did not. Although there were no statistically significant variations in IL-1β levels by sex, family history of epilepsy, seizure type, or EEG,

Similarly, it was found that patients with extremely high cytokine levels (such as IL-1beta, IL-1R, IL-6, IL-8, IL-10, and TNF-alpha) experienced protracted (>1 h) unresponsive seizures that required the administration of more than two different classes of anticonvulsants [16].

Positive associations were found amongst IL-1β and only to the duration of fits in the current investigation; however, no statistically significant associations were found amongst IL-1β or any of the demographic or clinical variables examined.

Consistent with the findings of reported that IL-1β levels in the peripheral blood of children with intractable temporal lobe epilepsy were higher than those in the control group ($t = 2.813$, $P = 0.01$) and our results were in agreement with who observed that there was a linear correlation between these levels and the duration of single seizures ($r = 0.9735$, $P < 0.05$) but not with the duration of the disease [17].

In animal models of epilepsy, IL-1β has been shown to both precipitate and be generated in response to seizures. By increasing excitatory neurotransmission and decreasing inhibitory GABA-mediated neurotransmission,IL-1β [18] may cause seizures. [19] Mice as young as 2 weeks old can have convulsions when injected with IL-1β intracerebrally during a fever [20].

Conclusion

The results of this research revealed no statistically significant variance amongst interactable epileptic patients and controlled epilepsy patients concerning IL-1β level. However, IL-1β could detect epileptic patients with prolonged seizures and there was a significant positive association between IL-1β and the duration of fits.

Conflict of interest

None of the contributors declared any conflict of interest.

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