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Diagnostic Value of Interleukin 1 Receptor Antagonist (IL-1RA) in Children with Refractory Epilepsy

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ABSTRACT
Background: Clinical studies have shown that prolonged seizures result in increased cytokine production in the central nervous system. **Aim of work:** To focus on diagnostic value of interleukin-1 receptor antagonists in refractory epilepsy.
Patients and methods: This case-control investigation was done in Pediatric Neurology Unit and Pediatric Neurology Clinics, Faculty of Medicine, Zagazig University. Children were classified into: patient group: 59 children with refractory epilepsy aged between 1 year and 16 years old and control group: 59 healthy children who are age and sex corresponded to the patient population. Serum level of IL-1Ra was assessed. **Results:** There is significant higher value of plasma of interleukin1 receptor antagonist in studied refractory epilepsy group compared to the healthy control group.
Conclusion: Interleukin-1 receptor antagonist can differentiate the control group and the seizure group.
Keywords: IL-1RA, Refractory Epilepsy, diagnosis.

INTRODUCTION

Epilepsy is a chronic disease of the brain characterized by an enduring (i.e., persisting) predisposition to generate seizures and by the neurobiologic, cognitive, psychological, and social consequences of seizure recurrences [(1)].

Despite receiving competent medical care, more than 30% of all people with epilepsy experience uncontrolled seizures or adverse effects from medication.[(2)]. A condition known as refractory epilepsy is one where at least two antiepileptic drugs have not been able to prevent seizures. [(3)]. According to some sources, it raises the chance of damage, which then raises the likelihood of dying, as well as the possibility of cognitive and psychological problems. [(4)].

It is the immune system's intended to defend the host from threats that can come from both the outside (such as bacteria and viruses) and the inside (such as malignant transformation). [(5)].In general, cytokines are created and released in response to antigenic stimuli. Recently, it has been discovered that patients with seizures exhibit aberrant cytokine and immune cell expression. Numerous studies have demonstrated that the immune system controls the synthesis and release of cytokines, and that by acting as seizure mediators, these cytokines can worsen brain damage.[(6,7)].

Cytokines are soluble, powerful glycoproteins that play a role in the control of growth, activation of immune cells, and inflammatory and immunological responses. The glial cells in the CNS secrete them. Experimental research has demonstrated that epileptic seizures are associated with an increased generation of inflammatory cytokines. In this context, interleukin-1 (IL-1) cytokines are given a lot of attention.[(8-10)].

The IL-1 cytokine family consists of IL-1 alpha (IL-1α), IL-1 beta (IL1β) and IL-1 receptor antagonist (IL-1Ra), they all attach to the IL-1 receptor. IL-1 is primarily membrane-bound, whereas IL-1 is primarily secreted. Interleukin-1beta (IL-1β) while interleukin-1 receptor antagonist (IL-1Ra) is anticonvulsant and neuroprotective, appears to be proconvulsant and neurotoxic. [(11)]. Based on epileptogenic foci surgically excised from DRE patients, the IL-1 signaling pathway has been linked to the development of human epilepsy [(12, 13)]. Recent research has shown a connection between IL-1 and IL-1R1 levels and epilepsy severity. [(14-16)].

We therefore sought to focus on diagnostic value of interleukin-1 receptor antagonists in refractory epilepsy.

PATIENTS AND METHODS

This Case-control study was done in Pediatric Neurology Unit and Pediatric Neurology Clinics, Faculty of Medicine, Zagazig University.

Population:
Children attending at pediatric inpatient and outpatient clinic were classified into:

- **Patient group:** 59 Children with refractory epilepsy diagnosed as having at least two effective antiepileptic medications without success, and the patients are taking their antiepileptic medications as prescribed. They aged between 1 year and 16 years old.
- **Control group:** 59 Healthy children who are age and sex matched with the patient group.

Inclusion criteria:

- Both sexes were included
- Patients diagnosed as having refractory epilepsy when at least two antiepileptic drugs that are efficient have not been able to manage seizures,

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and the patients are taking their antiepileptic medications as prescribed. (AEDs).

- Children aged between (1-16) years.

Exclusion criteria:

- Patient refusing to participate in the study
- Patients who have experienced serious medication reactions.
- Patients who don't take their AEDs as prescribed.
- Patients with severe mental or psychiatric illness.
- Patients who have a systemic illness (uncontrolled diabetes mellitus, hypertension, renal, liver, neoplastic, connective tissue disorders, morbid obesity, and anemia).

Method:

All patients were subjected to the following:

A thorough history taking that covers the duration of the condition, the frequency of attacks, the symptoms experienced by the patient, the signs noticed by onlookers during seizures, and the International League against Epilepsy's classification of epileptic seizures. Medical examination includes different systems assessment to exclude any associated medical illness.

Neurological evaluation, including the form currently in use by the paediatric neurology department.

Laboratory investigations including complete blood count, tests of kidney and liver function, serum sodium, potassium, and calcium and magnesium, C-reactive protein and serum level of IL-1Ra.

The IL-1Ra kit used a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) (BioKit, China).

to assay the level of Human Interleukin 1 receptor antagonist (IL-1ra/CD121) in samples. Interleukin 1 receptor antagonist (IL-1ra/CD121) was added to monoclonal antibody Enzyme well which is pre- coated with Human Interleukin 1 receptor antagonist (IL-1ra/CD121) monoclonal antibody, incubation; then, Interleukin 1 receptor antagonist (IL-1ra/CD121) antibodies labeled with biotin was added, and The uncombined enzyme was then removed after a second round of incubation and washing after combining with Streptavidin-HRP to produce an immunological complex. Following the addition of Chromogen Solutions A and B, the liquid's colour changed to blue before turning yellow under the influence of acid. The human substance interleukin concentration and the colour chroma 1 receptor antagonist (IL-1ra/CD121) of sample were positively correlated. Blank well was taken as zero, the optical density (OD) was measured under 450 nm wavelength which was carried out within 15min after adding the stop solution.

- **Radiological investigations:**

✓ **Magnetic Resonance Imaging:** As per ILAE recommendations, [17]the following MRI procedures were carried out: Axial and coronal T2-weighted sequences, fluid attenuated inversion recovery (FLAIR) sequences, thin slice (4–5 mm) volumetric T1–weighted gradient–recalled echo sequences, and high resolution oblique coronal T2-weighted imaging of the hippocampus were all used. Comparing the 3 T-MRI brain to the standard 1.5 T-MRI brain, better image signal-to-noise and contrast-to-noise ratios were achieved. It might increase the neuroimaging yield. [18]It is particularly beneficial in cases of suspected cortical development anomalies.

✓ **EEG:** EEG examination where encephalographic epileptiform abnormalities were detected and recorded in each EEG.

Administrative Design:

Study protocol was submitted for approval by the faculty medicine institutional review board (IRB) at Zagazig University. For each participant that shared the study with their parents, signed informed consent was obtained. The Declaration of Helsinki was followed in the conduct of the study.

Statistical Analysis: SPSS (Statistical Package for the Social Sciences) version 24 was used for data analysis. Means and standard deviations were used to characterize quantitative variables.

RESULTS

Table (1): Demographic characteristics of the studied groups

	Studied groups		Test of sig	p-value
	Refractory epilepsy group (N=59)	Healthy control group (N=59)		
Age (year) Mean ± SD Median (range)	 10.6±2.5 11(2-15)	 10.2±3.3 10(5-15)	**t** 0.72	0.47
Sex Males Females	 32 (54.2) 27 ((45.8)	 29(49.2) 30(50.8)	**χ 2** 0.305	0.58

Table 1 shows that there is no statistically difference between Refractory epilepsy group and control group regarding to age and sex p>0.05.

Table (2): Clinical manifestations in studied Refractory epilepsy group

	Variable	Refractory epilepsy group n.59	
		No.	%
	Positive family history	16	27.1%
Disease duration per years	Mean ± SD Median (range)	2.7 ± 1.5 3 (6 months-9 years)	
Number of attack in month	Mean ± SD Median (range)	5.6 ± 0.58 6 (2 -6)	

Table 2 shows that, the median of disease duration was 3 years and ranged from (6 months-9 years) years. The median of epilepsy attack in month was 6and ranged from (2-6). Positive family history recalled with 27.1% of patients.

Table (3): Laboratory finding in studied Refractory epilepsy group

Laboratory data	Refractory epilepsy group n.59	
	Mean ±SD	Median(range)
WBCs	8.5±1.7	8.5(4-11.3)
RBCs	4.3±0.53	4.3(2.8-5.4)
Hemoglobin	12.1±0.89	12.3(9.5-14.3)
PLT	314.3±75.3	297(189-510)
ALT	23.5±5.9	23(12.5-35)
AST	15.4±5.6	14(8.2-30)
Urea	13.7±4.2	13(6.5-26)
CREAT	0.58±0.24	0.53(0.23-1)
Na	138.6±3.8	138(129-148)
K	4.4±0.7	4.5(3.2-5.4)
Mg	1.98±0.28	2(1.34-2.78)
Ca	9.1±1.03	9.1(6.8-12)
CRP	2.4±0.98	2.5(0.6-4.72)

Table 3 reveals mean and range of studied laboratory finding for studied epileptic patients.

Table (4): Investigation of studied Refractory epilepsy group (n=59):

Investigation		Refractory epilepsy group n.59	
		n.	%
MRI	**Normal**	16	27.1
	Hypoxic lesion	43	72.9
EEG	**Normal**	5	8.5
	Abnormal	54	91.5

Table 4, reveals 72.9% of patients had Hypoxic lesion via MRI and 91.5% of patients had abnormal EEG finding.

Table (5): Plasma level of interleukin1 receptor antagonist in studied refractory epilepsy group and healthy control group

	Studied groups		U	p-value
	Refractory epilepsy group (N=59)	healthy control group (N=59)		
IL1Ra Mean ± SD Median (range)	221.7±20 210(8.05-536.3)	113.6±6.2 107.5(5.04-199.12)	5.7	0.0001 (HS)

Table 5, shows there is significant higher value of plasma of interleukin1 receptor antagonist in studied refractory epilepsy group compared to healthy control group $p < 0.05$.

Table (6): Correlation between interleukin1 receptor antagonist and age, disease duration, number of attacks per month, WBC, RBCs HB, Plt, ALT, AST, urea, serum creatinine, Na, K, Mg, Ca, CRP in studied refractory epilepsy group (n=59):

	Interleukin1 receptor antagonist	
	r	p
Age	0.046	0.623
Disease duration	0.084	0.526
Number of attacks per month	0.13	0.17
WBC	-.046-	0.731
RBCs	0.04	0.762
HB	-.132-	0.32
Plt	-.028-	0.831
ALT	-.056-	0.671
AST	-.054-	0.683
Urea	**-.258-***	**0.049**
Creatinine	-.056-	0.675
Na	-.054-	0.685
K	-.051-	0.699
Mg	-.170-	0.198
Ca	-.037-	0.783
CRP	0.008	0.955

(r) correlation coefficient ** Correlation is significant at the 0.01 level, * Correlation is significant at the 0.05 level

Table 6 shows that there is significant inverse relation between interleukin1 receptor antagonist and blood urea. Otherwise, there is no relation between other parameters**.**

Table (7): Performance interleukin1 receptor antagonist (ILRa) in diagnosis refractory epilepsy

Cut off level (ILRa)	Sensitivity	Specificity	PPV	NPV	Accuracy	Youden index
≥ 99.5	88.1%	42.4%	60.5%	78.1%	65.3%	0.305
≥ 146.8	76.3%	67.8%	70.3%	74.1%	72%	0.441
≥ 195.5	62.7%	86.4%	82.2%	69.9%	74.6%	0.491

Table 7 shows that Interleukin1 receptor antagonist (ILRa) at a cutoff value of ≥ 99.5 which use for diagnosis refractory epilepsy revealed a sensitivity of 88.1%, a specificity of 42.4% and 65.3% accuracy. Where interleukin1 receptor antagonist (ILRa) at a cutoff value of ≥ 146.8 use for diagnosis refractory epilepsy revealed a sensitivity of 76.3%, a specificity of 67.8% and 72% accuracy. Whereas Interleukin1 receptor antagonist (ILRa) at a cutoff value of ≥ 195.5 for diagnosis refractory epilepsy revealed a sensitivity of 62.7% a specificity of 86.4% and 74.6% accuracy. It obvious that best interleukin1 receptor antagonist (ILRa) value for diagnosis refractory epilepsy cases, was ≥ 195.5.

DISCUSSION

Our results demonstrated that regarding age and sex, there is no statistically substantial variation between the groups with refractory epilepsy and the controls.

In line with our research, **Schreiber *et al.*** [19]found that there was no statistically significant difference in age or sex between the control group and the group with refractory epilepsy. Also, **El-Rashidy *et al.*** [20] found the same results.

Regarding clinical manifestation, the median of disease duration was 3 years and ranged from (6 months-9 years) years. The average monthly number of epilepsy attacks was 6, and they ranged from (2—6). Positive family history recalled with 27.1% of patients.

El-Fayoumy *et al.* [21] reported that the mean of epilepsy attack per month was 2.2. and positive family history recalled with 13.3% of patients. **Klotz *et al.*** [22] found that the frequency of attack per month was 3 attacks.

Uludag *et al.* [23] demonstrated that seizure frequency was 13 ± 16.27 seizures per month.

In the current study, the mean WBCs was 8.5±1.7, RBCs 4.3±0.53, hemoglobin 12.1±0.89, PLT 314.3±75.3, ALT 23.5±5.9, AST 15.4±5.6, Urea 13.7±4.2, CREAT 0.58±0.24, Na 138.6±3.8, K 4.4±0.7,

Mg 1.98±0.28, Ca 9.1±1.03, and CRP 2.4±0.98. all laboratory investigations were within normal range.

This came in agreement with **Priskila and Suwarba,** [24] who found that The results of the tests for electrolytes, renal function, complete blood count, and liver function were all normal. range, according to the laboratory inquiry.

Yoo, K. H., & Yim, [25] found that Results from the lab showed that the white blood cell count 10,400/μL, hemoglobin 8.5 g/dL, and platelets 466×103 /μL. Other parameters were AST 64 IU/L, ALT 40 IU/L, urea 33.7 mg/dL, creatinine 1.08 mg/ dL, sodium 144 mEq/L.

We demonstrated that 72.9% of patients had hypoxic lesion via MRI, and 91.5% of patients had abnormal EEG finding.

In agreement with our study, **Alapirtti *et al.*** [26] found that 27.3% of patients had normal MRI while 72.7% of patients had abnormal lesion.

Aneja and Jain, [27] reported that the modality of choice for a child with refractory epilepsy during the initial assessment is brain magnetic resonance imaging (MRI).

Singh *et al.* [28] reported that refractory exclusion of structural pathology is necessary for epilepsy. It is important to take another look at earlier neuroimaging results (such as diffuse low-grade glioma and multifocal abnormality of cortical development) might not have any therapeutic ramifications, but they do help to explain why epilepsy is so refractory. Sometimes a sudden vascular disease leads to the investigation of a treatable underlying cause, such as antiphospholipid syndrome.

Our results revealed that there is significant higher value of plasma of interleukin1 receptor antagonist in studied refractory epilepsy group compared to healthy control group.

In agreement with our study, **Clarkson *et al.*** [29] demonstrated that IL1RA was elevated in epilepsy serum compared to control**.**

In addition, **Takamatsu *et al.*** [30] found that the epilepsy group had significantly higher percentages of interleukin-1 receptor antagonist (IL-1RA) than the control group.

Also, **Yamanaka *et al.*** [16] found that epilepsy patients had a significantly higher percentage of IL-1 receptor antagonist than controls.

The study results revealed that there is substantial inverse link between interleukin1 receptor antagonist and blood urea. Otherwise, there is no relation between other parameters (age, disease duration, number of attack in month, WBC, RBCs, HB, Plt, ALT, AST, serum creatinine, Na, K, Mg, Ca, and CRP).

In agreement with our study, **Alapirtti *et al.*** [26] demonstrated that there is no link between the production of IL-1Ra and the clinical features of epilepsy was found**.**

In addition, **Uludag *et al.*** [23] demonstrated that baseline IL1R levels were not correlated with the frequency of seizures.

Regarding performance interleukin1 receptor antagonist (ILRa) in diagnosis refractory epilepsy, the results revealed a sensitivity of 88.1%, a specificity of 42.4% and 65.3% accuracy at a cutoff value of ≥ 99.5. Where interleukin1 receptor antagonist (ILRa) in diagnosis refractory epilepsy revealed a sensitivity of 76.3%, a specificity of 67.8% and 72% accuracy at a cutoff value of ≥ 146.8. Moreover, Interleukin1 receptor antagonist (ILRa) in diagnosis refractory epilepsy revealed a sensitivity of 62.7% a specificity of 86.4% and 74.6% accuracy at a cutoff value of ≥ 195.5.

The results explored that interleukin1 receptor antagonist (IL1Ra) at cut off value ≥ 99.5 valid for detecting refractory epilepsy cases. While interleukin1 receptor antagonist (ILRa) at cut off value ≥ 195.5valid for exclude refractory epilepsy cases.

In agreement with our study, **Youn *et al.*** [8] reported that IL-1Ra can differentiate between the seizure group and the control group.

Additionally, it was shown that IL-1Ra has been proven to be a potent seizure predictor in a variety of seizure models. Seizures trigger the production of IL-1Ra many hours after IL-1 to quickly reverse its effects. It is important to note that IL-1Ra expression peaked later than the inflammatory cytokines did in the rodent brain (24 hours vs. 6 hours). Peak levels of the pro-inflammatory cytokine (IL-1, IL-6, and TNF-) and anti-inflammatory cytokine (IL-1Ra) effects occurred 6 hours, 24 hours, and 48 hours following status epilepticus (SE), respectively. The IL-1 system is activated in response to seizures, and IL-1Ra limits the proinflammatory effects of IL-1.[31].

CONCLUSION

Interleukin-1 receptor antagonist can differentiate the seizure group and the control group. It has been shown to be a powerful predictor of refractory epilepsy.

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