Original Research Article

Study The Role of Pro-inflammatory Cytokines (Interleukin 1-Beta, Interleukin 6) and High Sensitivity C-Reactive Protein in Children with Refractory Epilepsy

Abstract

Background: The International League Against Epilepsy (ILAE) has defined epilepsy as a status in which at least two unprovoked (or reflex) seizures happening for more than 24 hours part, or it can involve one unprovoked seizure if there is a recurrence possibility over the subsequent 10 years, or if the patient has been diagnosed by epilepsy syndrome. A failure of seizures controlling with at least 2 or more antiepileptic drugs for at least 2 years with good compliance and adequate serum therapeutic drug levels with a minimum frequency of seizures with no more than 3 months of free seizures was the definition of refractory epilepsy**.**

Methods: This case control research was conducted on 130 children selected from the outpatient clinic of pediatric neurology. They were divided into three groups: group I with refractory epilepsy, group II with controlled idiopathic epilepsy and group III were healthy children. All children enrolled in the study were subjected to the following: routine laboratory investigations (serum antiepileptic drugs, complete blood count and liver and renal function tests) and specific laboratory investigations (estimation of serum interleukin-6, IL-1β and hs-CRP) electroencephalography (EEG), brain magnetic resonance imaging (MRI).

Results: Interleukin -6, interleukin -1 beta and high sensitivity C-reactive protein serum levels were significantly higher in refractory epilepsy children, than in those with controlled epilepsy and the control children ($P<0.001$). IL-6, IL-1β and hs-CRP serum levels showed no significant difference in children with controlled epilepsy in comparison to healthy control children ($P>0.05$).

Conclusions: The production of IL-1β, IL-6 and hs-CRP has been increased in the serum of refractory epilepsy children. Our findings suggest that this systemic inflammatory reaction with increasing IL-6, IL-1β and hs-CRP mean serum levels are effective biomarkers for epileptogenesis in the children and may contribute to refractory epilepsy and potentially can be correlated with the severity and prognosis of the disease.

Keywords: Refractory Epilepsy, Pro-inflammatory cytokines, Interleukin 1-Beta, IL-6, hs-CRP

Introduction:

The International League Against Epilepsy (ILAE) has defined epilepsy as a status in which two unprovoked (or reflex) seizures at least are happening for more than 24 hours part, or one unprovoked seizure involved if there is a recurrence probability over the subsequent 10 years, or if the patient has been diagnosed with epilepsy syndrome. Seizure is a transient disorder of the function of the brain because of abnormal synchronous or excessive neural activity in varying degrees in the brain different anatomic regions [1].

Depending on pathogenesis, epilepsy is classified in 2017 by ILAE into six types: genetic, infectious, metabolic, immune, structural and unknown, these classifications may have an effect on epilepsy therapy, and they substitute the earlier labels idiopathic, symptomatic, and cryptogenic epilepsy; however, the cause may be multiple [2, 3].

Refractory epilepsy is well-developed when seizure control is inadequate despite the utilization of two AEDs which were potentially effective within tolerable levels for 2 years and non-epileptic events or poor compliance was excluded [4].

Refractory epilepsy in children can lead to psychiatric problems involving depression, cognitive delay and poor school performance, sleep or mood disorders drug interactions due to polytherapy and also risk of drug toxicity [5].

For several decades, in childhood epilepsy, the immune system and the inflammation functional roles t have been suggested as pediatric autoimmune and infectious diseases are often associated with recurrent seizures, additionally, immunotherapy is an effective treatment for refractory seizures in some paediatric epilepsy syndromes [6].

Glial cells can be stimulated by the precipitating factor, such as brain insult, releasing pro-inflammatory mediators, initiating inflammatory processes cascade resulting in epilepsy and seizures , blood brain barrier disruption may be included in both the initiation of seizures and

the progression to epilepsy where immune cells and inflammatory molecules may cross the brain to blood and vice versa [7].

Pro-inflammatory cytokines are heterogeneous polypeptide compounds which act primarily as inflammatory signals mediators in peripheral tissues. Increased production of inflammatory cytokines has been established in experimental models in conjunction with epileptic seizures; interleukin-6 (IL-6) and interleukin-1 (IL-1) get considerable attention in this regard. The family of IL-1 cytokine is composed of IL-1 receptor antagonist (IL-1RA), IL-1 alpha, IL-1 beta (IL-1β) IL-1β is neuro-protective in low concentrations but in pathological circumstances, IL-1β high levels result in proconvulsant and neurotoxic effects, thus it is accompanied by epileptogenesis and seizure susceptibility. IL-6 is increased in several neurological disorder where it is chronically increased in patients with epilepsy. IL-6 chronic over expression is accompanied by spontaneous seizures development [8-10].

The high sensitivity C-reactive protein (hs-CRP) is an effective biomarker for the detection of mild, chronic inflammation that is not determined by values of conventional CRP. Evidence accumulating from human research and experimental models suggests that epilepsy pathophysiology includes inflammatory mechanisms [11].

concentrations of CRP were detected in individuals with tonic clonic seizures who were not previously diagnosed and treated with no evidence of central nervous system or systemic infections [9].

This research aimed to assess the inflammation role in refractory epilepsy children aiming to determine the hs-CRP and pro-inflammatory cytokines [IL-6, IL-1β) production in refractory epilepsy children and to explore the relationship between cytokines production and seizure frequency in children with refractory epilepsy.

Patients and Methods:

This case control research was conducted in Tanta University Hospital, Pediatric Department, Neuropsychiatry Unit, during the study period over two years from April 2019 to April 2021. It included 80 children with epilepsy selected from the outpatient clinic of pediatric neurology with the age range (5-16 years), 64 male and 16 females. They were classified into three groups: group Included 30 children having refractory epilepsy depending on the criteria of Beleza et al.[4]as they received 2 or more antiepileptic drugs for at least 2 years with good compliance and adequate serum therapeutic drug levels with a recurrence rate was at least once per month with no more than three months of free-seizures in this period, normal developmental history, normal neurological examination, MRI brain findings were normal and most of the cases have positive family history, group II included controlled 50 children with controlled idiopathic epilepsy diagnosed depending on the International League Against Epilepsy (ILAE, 2010) criteria with at least 2 unprovoked seizures occurring >24 hours part without fever or acute cerebral insult [12], they received one or two antiepileptic drugs for 2 years with good compliance and adequate serum therapeutic drug level, had no seizures for two years, normal developmental history, normal neurological examination, MRI brain findings were normal and most of the cases had positive family history and group III was a control group included 50 healthy children..

An informed written consent was obtained from the guardians or relatives of the patients. The research was done after approval from the Ethical Committee Tanta University Hospitals.

We excluded children with any neurological diseases, children with inborn errors of metabolism, intellectual disability and hypotonia that may indicate genetic syndrome, congenital anomalies or CNS malformations, suggested features of dysmorphism, microcephaly, with renal, hepatic, chronic inflammation, autoimmune diseases or any chronic conditions, affecting the nervous system, with no history of any drug intake for at least three months before the study and also non-epileptic events.

All children enrolled in the research underwent the following: Full history taking, clinical examination, laboratory investigations (routine and specific investigations), electroencephalography (EEG), brain magnetic resonance imaging (MRI).

Estimation of serum interleukin-6: By using enzyme-linked immune-sorbent assay technology (ELISA) kit with catalogue number (201-12-0091-48T) provided by Biokit Company. Human interleukin 6 (IL-6) ELISA kit was on the basis of standard sandwich ELISA, a monoclonal antibody enzyme has been precoated onto 96-well plates with human IL-6 monoclonal antibodies, incubated then IL-6 labelled with biotin and have been coupled with Stretavidin-HRP to form immune complex then incubated and washed again after that chromogen solution has been added, the liquid's colour changed to blue and then to yellow under the influence of acid. The chroma of the samples was positively correlated with the concentration of the human chemical IL-6.

Estimation of IL-1β: By using ELISA kit with catalogue number (201-12-0144) provided by Biokit Company. Human interleukin 1 beta (IL-1β) ELISA kit was based on standard sandwich ELISA a monoclonal antibody enzyme has been precoated onto 96-well plates with human IL-1β monoclonal antibodies, incubated then IL-1β antibodies labelled with biotin and have been combined with Stretavidin-HRP then incubated and washed again, after that chromogen solution has been added, the liquid's colour changed to blue and then to yellow under the influence of acid. The chroma of the samples was positively correlated with the concentration of the human IL-1β substance.

Estimation of hs-CRP: By using ELISA kit with catalogue number (201-12-1806) provided by Biokit. High sensitivity CRP (hs-CRP) were based on standard sandwich ELISA. A monoclonal antibody enzyme has been precoated onto 96-well plates with hs-CRP monoclonal antibodies, incubated then hs-CRP antibodies labelled with biotin and have been combined with Stretavidin-HRP then incubated and washed again, after that chromogen

solution has been added, the liquid's colour changed to blue and then to yellow under the influence of acid. The chroma of the samples was positively correlated with the concentration of the human substance hs-CRP.

Statistical analysis

SPSS v26 (IBM Inc., Chicago, IL, USA) was used for statistical analysis. Quantitative variables were presented as mean and standard deviation (SD) and ANOVA (F) test was used to compare between the two groups. Chi-square test was used to analyse qualitative variables which were presented as frequency and percentage (%). A two tailed P value < 0.05 was considered statistically significant. Pearson correlation was done to estimate the degree of correlation between two quantitative variables. Linear Correlation coefficient (r) was used for detection of correlation between two quantitative variables in one group.

Results:

As regard age and sex, there was no significant difference between control and patients. as regard family history, there was no significant difference between children with refractory and controlled epilepsy. Table 1

The IL-6, IL-1β and hs-CRP mean serum levels were significantly higher refractory epilepsy children than those with controlled epilepsy and the control children (P<0.001). Additionally, the IL-6, IL-1β and hs-CRP mean serum levels showed no significant difference in children with controlled epilepsy in comparison to healthy control children (P>0.05). Table 2

Children treated with more than two AEDs had significantly higher IL-6, IL-1β and hs- CRP mean serum level of than children treated with two AEDs (p-value<0.05). Table 3

There was no significant relation between types of seizures and the IL-6, IL-1β and hs-CRP mean serum levels (P>0.05). Children with high frequency of seizures (daily seizures) had

significantly higher mean serum levels IL-6, IL-1β and hs-CRP than children with one seizure per week (P-value<0.05). Table 4

There was a significant positive correlation between the IL-6, IL1β and hs-CRP mean serum level and the duration of epilepsy in years. The longer the duration of epilepsy in years, the higher the mean serum level IL-6, IL1β and hs-CRP level in children with refractory epilepsy (r=0.505, 0.405 and 0.401) (p-value<0.05). Table 5

There was a significant positive correlation between the IL-6 mean serum level and the hs-CRP mean serum level. The higher the IL-6 serum level, the higher the hs-CRP serum level (r=0.444) (p- value<0.05). There was no significant correlation between the IL-1B mean serum level and the hs-CRP mean serum level. Table 6

Discussion

Pro-inflammatory cytokines can both modulate the inflammatory response and influence the development of the CNS. , They are frequently pleiotropic and their actions are dependent on specific cell membrane receptors presence; they are critical for the proper functions of both the adaptive and innate immune response; however, they also play a significant role in a series of CNS disorders related to and infection, including epilepsy [13].

In the present research the IL-6, IL-1β and hs-CRP mean serum concentrations were significantly higher in refractory epilepsy children than those with controlled epilepsy and the control children but no statistically significant difference between the children with controlled epilepsy and the healthy control children was detected.

Also these results in line with the results reported by Bartolini et al. [14] who had studied plasma cytokines levels including IL-6 and IL1β in 36 children had chronic epilepsy and new onset seizures with the age range was (1 month-18 years) and reported that the IL-6 plasma level was significantly higher in epileptic patients with both chronic epilepsy new onset seizures and then control children indicating its role in epileptogenesis and progression to

epilepsy but in contradictory to the results of this study the IL-6 serum level was more significantly increase in new onset seizure also in contradictory to this study the serum IL1β level was overall low and not significantly different between controls and cases of both chronic epilepsy and new onset seizures, this difference might be related to fewer number of cases or different timing of sampling or suggesting that IL-1β or IL-6 may have neuroprotective roles rather than proconvulsant effect in the brain in a certain time during the illness.

On the other hand, contradictory to our results, Saengow et al. [15] who had studied plasma level of IL-1β in 18 children with drug- resistant epilepsy with the mean age range was (12.6 ± 5.1years) and the results showed that the plasma IL-1β was significantly decreased in children with drug- resistant epilepsy than the healthy control children. This difference could be explained by this study as they suggested that IL-1β has a neuroprotective and anticonvulsant role rather than proconvulsant effect in the brain.

In the present study the hs-CRP, IL-6 and IL-1β mean serum levels were significantly higher in refractory epilepsy children who presented with daily seizures than those with one seizure per week.

In line with our study, Kamaşak et al. [16] who had studied the IL-1β serum level of in children with at least one episode of seizure per week and those with no seizures in the last year and found a significant increase in the IL-1β serum level in children with more frequent seizures than those with less frequent seizures.

This study showed that the IL-6, IL-1β and hs-CRP mean serum levels were significantly higher with longer duration of epilepsy and more seizures frequency indicating that more increase in peripheral production of cytokines with ongoing neuroinflammation may correlate with longer duration of epilepsy and more seizures frequent and suggesting that the serum

levels of cytokines may be an effective predictive and prognostic biomarker in children with drug -resistant epilepsy for seizure relapse and response to therapy.

In the present research, children treated with more than two AEDs had significantly higher IL-6, IL-1β and hs-CRP mean serum levels than children treated with two AEDs, a significant positive correlation between the duration of epilepsy in years and the IL-6, IL-1β and hs-CRP mean serum levels was found, the longer the duration of epilepsy in years, the higher the mean serum levels IL-6, IL-1β and hs-CRP in refractory epilepsy children.

These results agree in line with the results obtained by Ishikawa et al. [17] who had studied the correlation between the number of AEDs used in children and the frequency of seizures and found that number of AEDs in children with daily seizures were significantly greater than those with intermittent seizures and this was explained by the refractory clinical course of the daily seizures, also there was a significant increase of the IL-6 and hs-CRP mean serum levels in children with daily seizures with increasing the number of AEDs.

Also these results in accordance with the results collected by Choi et al. [18] who had demonstrated that the IL-1β serum level was significantly positive correlated with the AEDs numbers used in children with refractory epilepsy; however, in contradictory there was no significant difference between the duration of epilepsy in years and the mean serum levels IL-6 and IL-1β suggesting the variability of the effect of inflammatory cytokines in seizures etiopathology and progression with increased duration of epilepsy.

Contradictory to the results of this study, Prasad et al. [19] who had studied the correlation between epilepsy duration in years and number of AEDs in relation to the IL-6 mean serum level of in children with drug- resistant epilepsy and found no significant correlation and this might be related to the difference of the types and combination, duration and number of AEDs used that could affect the production of cytokines in variable ways.

Contradictory to the results of this study, Wu et al. [20] who had studied the correlation between the epilepsy duration in years and the IL-1β serum levels of in children with drug-resistant epilepsy and found no significant correlation, this might be explained by the difference in duration of epilepsy, number of patients, age onset of epilepsy and the duration and dosage of AEDs treatment between the different studies.

In the present research there was a significant positive correlation between the IL-6 mean serum level and the hs-CRP mean serum level. The higher the IL-6 mean serum level, the more the serum hs-CRP production indicating chronic inflammation in children with drug-resistant epilepsy.

In line with the result of this study, Elwan et al. [21] and Peltola et al. [22] had studied the correlation between the IL-6 mean serum level of and the CRP mean serum level of and found that the increase in IL-6 mean serum levels in turn induced production of CRP indicating chronic inflammation in these patients with refractory epilepsy but the results of this study were contradictory to Ishikawa et al. [17] who had found that the insignificant correlation between the IL-6 serum level and that of hs-CRP , and the variation of sampling time of both biomarkers in relation to seizures explained this difference. .

Limitations: Concentrations of hs-CRP may fluctuate slightly over time in response to subtle conditions, impairing the validity of CRP levels. There was no CSF or cortical tissue analysis of inflammatory markers. Another limitation is that the difference between this study's results and those of previous research may be due to the study's smaller sample size, variable time of sampling in relation to seizures, difference in the duration, types and combinations of AEDs taken, biological compartment analysed, or the immunoassay that was utilized.

Conclusions:

The production of IL-6, IL-1β and hs-CRP was increased in the serum of children with refractory epilepsy. Our findings suggest that this systemic inflammatory reaction with

increasing IL-6, IL-1β and hs-CRP mean serum levels are effective biomarkers for epileptogenesis in the children and may assist in drug-resistant seizure and potentially could be utilized as biomarkers to be correlated with the severity and prognosis of the disease.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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Table 1: Demographic data of studied groups.

		Group I (n=30)	Group II (n=50)	Control (n=50)	P-value
Age (years)		11.100 ±2.591	11.680±2.766	10.960±2.563	0.337
Sex	Male	20(66.67%)	44(88%)	41(82%)	0.062
	Female	10 (33.33%)	6 (12%)	9 (18%)	
Family history of epilepsy	Negative	4 (13.3%)	15 (30%)		0.090
	Positive	26 (86.7%)	35 (70%)		

Data presented as mean± SD or frequency (%)

Table 2: The mean serum levels of IL-6, IL-1β and hs-CRP in children with refractory epilepsy, children with controlled epilepsy and the control children.

	Group I(n=30)	Group II(n=50)	Group III(n=50)	P value		
IL-6 (pg/ml)	151.423± 38.978	6.992 ± 2.385	6.336 ± 2.37	<0.001*	P1	<0.001*
					P2	<0.001*
					P3	0.983
IL-1β (pg/ml)	2529.06 ± 1136.99	189.62±3.929	182.832±3.810	<0.001*	P1	<0.001*
					P2	<0.001*
					P3	0.998
hs-CRP (mg/L)	4.417±0.668	0.348±0.133	0.226±0.107	<0.001*	P1	<0.001*
					P2	<0.001*
					P3	0.169

Data presented as mean± SD, IL-6: interleukin -6. IL-1β: interleukin -1 beta. hs-CRP: high sensitivity C-reactive protein *: Significant as P value ≤0.005. P1: P value I&II, P2: P value I&III, P3: P value II&III.

Table 3: The mean serum level of interleukin -6, interleukin -1 beta and highly sensitive C- reactive protein among children with refractory epilepsy in relation to number of antiepileptic drugs (AEDs).

Group I	AE		P-value
	Two drugs	More than two drugs	
IL6 (pg/ml)	135.821±28.993	178.372±40.392	0.002*
IL1β (pg/ml)	2162.148±926.137	3162.818±1227.788	0.017*
hs-RP (mg/L)	4.200±0.593	4.791±0.644	0.017*

Data presented as mean± SD, IL-6: interleukin -6. IL-1β: interleukin -1 beta. hs-CRP: high sensitivity C-reactive protein. AE: Antiepileptic drugs *: Significant as P value ≤0.005.

Table 4: The mean serum levels of IL6, IL1β and hs-CRP among children with refractory epilepsy in relation to type of seizures, and Comparison of IL6, IL1β and hs-CRP among children with refractory epilepsy in relation to frequency of seizures.

		IL6 (pg/ml)	IL1β (pg/ml)	hs-CRP (mg/L)
Type of seizures	Generalized	153.176±35.407	2723.54±1118.15	4.461± 0.706
	Focal	145.661±51.923	1890.057 ±1021.09	4.271± 0.544
	P - value	0.663	0.090	0.520
Frequency/m	One seizure per week	121.826±23.824	1928.018±1106.697	4.009± 0.478
	Daily seizures	168.557± 35.878	2877.032±1026.526	4.653± 0.656
	P-value	0.001*	0.025*	0.008*

Data presented as mean± SD, IL-6: interleukin -6. IL-1β: interleukin -1 beta. hs-CRP: high sensitivity C-reactive protein. *: Significant as P value ≤0.005.

Table 5: Correlation between the mean serum level of IL6, IL1β and hs-CRP among children with refractory epilepsy in relation to duration of epilepsy in years.

Group I	Duration of epilepsy (years)	
	r	P-value
IL6 (pg/ml)	0.505	0.004*
IL1β (pg/ml)	0.405	0.026*
hs-CRP (mg/L)	0.401	0.028*

IL-6: interleukin -6. IL-1β: interleukin -1 beta. hs-CRP: high sensitivity C- reactive protein. *: Significant as P value ≤0.005. r: Pearson correlation.

Table 6: Correlation between the mean serum levels of interleukin -6, interleukin -1 beta and high sensitivity C-reactive protein among children with refractory epilepsy.

Group I	IL-6 (pg/ml)		IL-1β (pg/ml)	
	r	P-value	r	P-value
hs-CRP (mg/L)	0.444	0.014*	0.127	0.503

IL-6: interleukin -6. IL-1β: interleukin -1 beta. hs-CRP: high sensitivity C- reactive protein. *: Significant as P value ≤0.005. r: Pearson correlation.