RESEARCH ARTICLE

Association of interleukin-1 and interleukin-6 levels in lateralized temporal epilepsy patients

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Abstract

Objective: To explore the clinical significance of interleukin-1 and interleukin-6 in the development of lateralized temporal epilepsy.

Method: The prospective study was conducted from January to April of 2022 at the Neurology Department of Training and Research Hospital, Istanbul Medeniyet University, Turkey, and comprised patients with lateralized temporal epilepsy aged 18-86 years who were in the interictal period in group A and healthy controls in group B. The levels of interleukin-1 and interleukin-6 of patients in both groups were compared. Data was analysed using SPSS 25.

Results: Of the 92 subjects, 60(65.2%) were in group A; 35(58.3%) were males and 25(41.7%) were females with a median age of 37.5 years (interquartile range: 2.2-42.7 years). There were 32(34.8%) subjects in group B; 19(40.6%) females and 13(40.6%) males with a median age of 40.5 years (interquartile range: 25-50 years) ($p>0.05$). Within group A, 41(68.3%) patients had left-sided epilepsy and 19(31.7%) had right-sided epilepsy ($p<0.001$). Both interleukin-1 and interleukin-6 levels were lower in group A than in group B ($p<0.001$). Both interleukin levels did not significantly differ between right and left-lateralised temporal seizures ($p=0.44$). In the left-lateralized temporal seizures, interleukin-1 levels correlated with epilepsy duration ($p<0.006$), lower onset age ($p<0.050$), and presence of prenatal risk ($p<0.028$). Interleukin-1 and interleukin-6 levels were positively correlated with each other for lateralized temporal epileptic hemispheres ($p<0.001$).

Conclusion: Interleukin-1 level was correlated with epilepsy duration, lower onset age, and presence of prenatal risk in the left-lateralized temporal epilepsy.

Keywords: Focal epilepsy, Partial epilepsy, Lateralisation, Prognosis, Interleukin-1, Interleukin-6, Cytokine.

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Introduction

Epilepsy is caused by a series of complicated molecular and cellular cascades participating in neural inflammation, apoptosis, cytokine-mediated cytotoxicity, inflammation, oxidative stress (OS), and excitotoxicity.[1] Numerous variables contribute to the establishment of focal epilepsy and the related networks.[2] Many prognostic studies on focal epilepsy patients have been conducted.[2,3] The patients' clinical and electroencephalographic (EEG) characteristics, biomarkers, nutrition, and epilepsy surgery are important factors in prognosis assessment,[3,4] which is crucial, especially in the case of focal epilepsy. Identifying the appropriate therapy modalities for each patient, including epilepsy surgery, leads to successful treatment.

Microglial cells primarily produce inflammatory cytokines in the central nervous system (CNS). With the stimulation of endothelial cells, microglial cells produce pro-inflammatory cytokines.[5] As a result, the major generator of inflammatory cytokines, interleukin-1 (IL-1), is produced. The release of other cytokines, including IL-6, is promoted by the synthesis of IL-1.5 Animal studies have revealed differences in cytokine levels between hemispheres, with the right neocortex releasing IL-1 and IL-6 at a higher rate than the left neocortex.[6,7]

To our knowledge, there is no published data to compare the serum levels of IL-1 and IL-6 in temporal epilepsy patients with either left or right lateralization and to assess their clinical importance.

The current study was planned to fill the literature gap by comparing serum IL-1 and IL-6 levels in temporal epilepsy patients lateralized to the left or right hemispheres and to evaluate their clinical importance.

Patients and Methods

The prospective, observational, case-control study was conducted from January to April of 2022 at the Neurology Department of Training and Research Hospital, Istanbul Medeniyet University, Turkey. The sample comprised patients with lateralized temporal epilepsy aged 18-86 years who were in the interictal period in group A and healthy controls in group B. After approval from the ethics review committee, the patients were enrolled from among

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those who underwent video EEG monitoring (VEM) during the study period. Group A was subdivided into left lateralization group A1 and right lateralization group A2. The research comprised all patients monitored in the VEM unit and whose data were complete. Those with generalized epilepsy, multifocal focal epilepsy, and individuals with non-epileptic episodes were excluded. The patients were treated with a combination of 2-5 antiepileptic medications from among phenytoin, carbamazepine, valproic acid, levetiracetam, clonazepam, clobazam, lamotrigine, topiramate, and zonisamide.

The controls were non-smoking, healthy volunteers with no systemic or CNS disease, and were not on long-term medication. The control group was raised from among the relatives of the patients and hospital employees.

Demographic and clinical data was recorded, including age, gender, education, hand dominance, marital status, seizure frequency, parental consanguinity, epilepsy onset age, duration of epilepsy, intellectual disability, trauma, CNS infection, febrile convulsion history, and systemic disorders. Prenatal risk factors included low birthweight (LBW), preterm, toxin exposure, persistent maternal sickness, and certain maternal illnesses. Focal epilepsy patients' seizures lateralized to only one temporal lobe were confirmed with compatible results in brain magnetic resonance imaging (MRI), long-term video-EEG monitoring, and positron emission tomography-computed tomography (PET-CT). Interictal and ictal recordings were taken during the video-EEG monitoring of all group A patients.

The Helsinki Declaration's guiding principles were followed while conducting the study. Informed consent was obtained from all individual participants included in the study. Prof. Suleyman Yalcin of the Istanbul Medeniyet University and the Training and Research Hospital's Ethics Committee (date/protocol: 2021/0701) approved the research.

All subjects had their levels of IL-1 and IL-6 assessed. In group A, the assessment was done approximately one month after the last seizure. All patients were assessed in the interictal phase to guarantee uniformity in the sample. For IL-1 and IL-6 serum levels, 3 mL of venous blood

Table-1: Intergroup comparison of clinical and demographic characteristics.

	All patients (n=60) n (%)	**Control group** (n=19) n (%)	***p*-value**	**Right-sided epilepsy** (n=41) n (%)	**Left-sided epilepsy** (n=32) n (%)	***p*-value**
Age (years)	37.5 (26.2-42.7)	40.5 (25-50)	0.294*	37 (22-46)	38 (30-42)	0.545*
Gender			0,105†			0.606†
Female	25 (41.7)	19 (59.4)		7 (36.8)	18 (43.9)	
male	35 (58.3)	13 (40.6)		12 (63.2)	23 (56.1)	
Hand dominance			0.156†			0.705††
Right	51 (85)	31 (96.9)	†	17 (89.5)	34 (82.9)	
Left	9 (15)	1 (3.1)		2 (10.5)	7 (17.1)	
Education Status			0.001†			0.193†
Primary-	64.4	8 (25)		10 (52,6)	28 (70)	
middle	22	12 (37.5)		6 (31.6)	7 (17.5)	
University	13.6	12 (37.5)		3 (15.8)	5 (12.5)	
Marital Status			0.042†			0.322†
Married	26 (43.3)	21 (65.6)		10 (52.6)	16 (39)	
Single	34 (56.7)	11 (34.4)		9 (47.4)	25 (61)	
Duration of Epilepsy (years)	15 (7.2-30)			10 (6-20)	22 (10-33)	0.013*
Epilepsy onset age (years)	12.5 (5-21)			16 (12-34)	11 (3-18)	0.038*
Mental Retardation	15 (25)			2 (10.5)	13 (31.7)	0.070††
Perinatal risk	12 (20)			5 (26.3)	7 (17.1)	0.493††
Head trauma	16 (26.7)			6 (31.6)	10 (24.4)	0.550†
Central nervous system infection	4 (6.7)			1(5.3)	3 (7.3)	
Febrile Convulsion	28(46.7)			8 (42.1)	20(48.8)	0.630†
Aura	35(58.3)			9(47.4)	26(63.4)	0.241†
Parental consanguinity	14 (23.3)			5 (26.3)	9 (22.0)	0.749††
Therapy						0.05†
Monotherapy	24(40)			11(57.9)	13 (31.7)	
Polytherapy	36 (60)			8(42.1)	28 (68.3)	

*Mann Witney U test. †Pearson Chi-Square. ††Fisher's Exact Test was used to analyse the clinical and demographic features. Median, 25th percentile, and 75th percentile values. $p<0.05$ was considered statistically significant.

samples were drawn from all participants between 9 am and 11 am. Within the first 30 minutes after collection, the samples were centrifuged for 10 minutes at 1,000rpm at 2-8°C. The supernatants were collected, put into Eppendorf tubes, and kept there until analysis at -80°C. Human IL-1 enzyme-linked immunosorbent assay (ELISA) kit (Catalogue No. E0077Hu) ELABSINCE Houston Texas, USA and Human IL-6 ELISA kit (Catalogue No. E0090Hu) ELABSINCE Houston Texas, USA were used.

Data was analysed using SPSS 25. Kolmogorov-Smirnov and Shapiro-Wilk tests were used, as appropriate, to compare the groups and the subgroups. The homogeneity of group variances was tested using Levene's test. When the assumptions for the parametric test were met, an independent samples t-test was utilized, calculating the means and standard deviations. The median (25th-75th percentile interquartile range [IQR]) was specified when the guesses for the parametric test were not satisfied, and the Mann-Whitney U test was applied. Categorical variables were presented as frequencies and percentages. Pearson chi-square and Fisher's Exact tests were used to analyse differences between categorical variables. Spearmen's correlation coefficient was used for continuous and ordinal variables that did not have a normal distribution. The point-bi-serial correlation coefficient was applied for two categories and continuous variables. P<0.05 was considered significant.

Results

Of the 92 subjects, 60(65.2%) were in group A; 35(58.3%) were males and 25(41.7%) were females with a median age of 37.5 years (IQR: 2.2-42.7 years). Initially, 287 patients were assessed among whom 60(21%) met the inclusion criteria. The remaining sample comprised 32(34.8%) subjects in group B; 19(40.6%) females and 13(40.6%) males with a median age of 40.5 years (IQR: 25-50 years) (p>0.05). Compared to group A, higher levels of education (p=0.001) and higher proportion of married people (p=0.042) were

Table-2: Correlation of interleukin-1 (IL-1) and (IL-6) levels with clinical and demographic data in all focal epilepsy patients.

	Interleukin-1		Interleukin-6	
	***p*-value**	***r*-value**	***p*-value**	***r*-value**
Interleukin-1			**0.001***	**0.682***
Interleukin-6	**0.001***	**0.682***		
Age (years)	0.158*	-0.185*	**0.028***	**-0.284***
Gender	0.575**	0.074**	0.068**	0.605**
Duration of epilepsy (years)	**0.034***	**-0.274***	0.147*	-0.190*
Epilepsy onset age (years)	**0.024***	**0.291***	0.260*	0.148*
Trauma	0.836**	-0.027**	0.645**	0.061**
Central nervous system infection	0.392**	-0.112**	0.347**	-0.123**
Febrile Convulsion	0.843**	0.026**	0.641**	0.061**
Seizure Frequency (monthly)	0.663*	-0.057*	0.415*	-0.107*
Hand dominance	0.147**	-0.189**	0.124**	-0.201**
Perinatal risk	**0.016****	**0.310****	0.237**	0.155**
Mental Retardation	0.241**	-0.154**	0.280**	-0.142**
Longest seizure-free period	0.533*	0.083*	0.618*	0.066*
Therapy	0.409**	0.108**	0.452**	0.099**

*Spearsman's rho correlation analyses test and ** Pearson Correlation tests were used. (Median, 25th percentile, and 75th percentile values) p<0.05 was considered statistically significant.

Table-3: Correlation of interleukin-1 (IL-1) and (IL-6) levels with clinical and demographic data in lateralized focal epilepsy patients.

	Interleukin-1		Interleukin-6	
	***p*-value**	***r*-value**	***p*-value**	***r*-value**
Interleukin-1				
Right hemisphere			0.001*	0.810*
Left hemisphere			0.001*	0.605*
Interleukin-6				
Right hemisphere	0.001*	0.810*		
Left hemisphere	0.001*	0.605*		
Age (years)				
Right hemisphere	0.489*	-0.169*	0.438*	-0.189*
Left hemisphere	0.110*	-0.253*	0.058*	-0.299*
Gender				
Right hemisphere	0.847**	-0.048**	0.504**	-0.163**
Left hemisphere	0.366**	0.145**	0.243**	0.186**
Duration of epilepsy (years)				
Right hemisphere	0.329*	0.237*	0.504*	0.163*
Left hemisphere	0.006*	-0.419*	0.052*	-0.306*
Epilepsy onset age (years)				
Right hemisphere	0.929*	0.022*	0.729*	0.085*
Left hemisphere	0.050*	0.308*	0.303*	0.166*
Trauma				
Right hemisphere	0.367**	-0.219**	0.506**	-0.163**
Left hemisphere	0.541**	0.098**	0.185**	0.189**
Central nervous system infection				
Right hemisphere	0.597**	-0.130**	0.561**	-0.142**
Left hemisphere	0.526**	-0.102**	0.491**	-0.111**
Febrile Convulsion				
Right hemisphere	0.813**	0.058**	0.211**	0.301**
Left hemisphere	0.900**	0.020**	0.708**	-0.060**
Seizure Frequency (monthly)				
Right hemisphere	0.639*	0.115*	0.820*	0.056*
Left hemisphere	0.960*	-0.08*	0.457*	-0.119*
Hand dominance				
Right hemisphere	0.480**	-0.173**	0.395**	-0.207**
Left hemisphere	0.218**	-0.197**	-0.189**	0.213**
Perinatal risk				
Right hemisphere	0.298**	0.252**	0.859**	0.044**
Left hemisphere	0.028**	0.343*	0.189*	0.209**
Mental Retardation				
Right hemisphere	0.492**	-0.168**	0.395**	-0.207**
Left hemisphere	0.448**	-0.122**	0.598**	-0.085**
Longest seizure-free period				
Right hemisphere	0.781*	-0.068*	0.695*	-0.096*
Left hemisphere	0.520*	0.105*	0.545*	0.099*
Therapy				
Right hemisphere	0.604**	0.127**	0.972**	-0.009**
Left hemisphere	0.764**	0.048**	0.463**	0.118**

*Spearsman's rho correlation analyses test and **Pearson Correlation tests were used. (Median, 25th percentile, and 75th percentile values) P<0.05 was considered statistically significant.

seen in group B. Within group A, 41(68.3%) patients were in subgroup A1 with left-sided epilepsy and 19(31.7%) were in A2 with right-sided epilepsy (p<0.001) (Table 1).

The median IL-1 level in group A was 13.8ng/L (IQR: 9.5-41.7ng/L) compared to 39.6ng/L (IQR: 19.8-74.7ng/L) in group B (p<0.001). Median IL-1 level was 10.9ng/L (IQR: 9.5-14.1ng/L) in group A1, and it was 13.1ng/L (IQR: 11.1-41.7ng/L) in A2. The median IL-6 level was 15ng/L (IQR: 8.4-65.5ng/L) in group A compared to 48.4ng/L (IQR: 15.5-80.8ng/L) in group B (p<0.001). Median IL-6 level was 12.5ng/L (IQR: 8.4-16ng/L) in A1, and it was 12ng/L (IQR: 8.5-65.5ng/L) in A2. There was no significant difference in IL-1 and IL-6 levels for lateralized epileptic temporal hemispheres (p>0.05).

When comparing lateralized temporal epileptic hemispheres, IL-1 and IL-6 levels were positively correlated (p<0.001) (Table 2). In group A1 patients, IL-1 was also correlated with epilepsy duration (p=0.006), epilepsy onset age (p=0.05), and the presence of prenatal risk (p=0.028) (Table 3).

In terms of age, head trauma, CNS infection, and febrile convulsion history, there was no significant difference between A1 and A2 patients (p>0.05).

Discussion

Cytokine production is an immune hallmark crucial in the development and progression of epileptic seizures.[5,6,8,9] IL-1 and IL-6 are the most studied cytokines, especially in focal epilepsies.[10] In hypoxia-induced epilepsy, IL-1 is responsible for the development of epilepsy.[11] Although the different effects of IL-1 and IL-6 in temporal and extra-temporal focal epilepsy have been studied,[12] there is no study, to our knowledge, on their involvement in lateralized temporal epilepsy comparing the right and left hemispheres. In the current study, which also compared the two hemispheres, all patients with temporal epilepsy had considerably lower IL-1 and IL-6 levels than the control group. The low levels of these ILs resulted probably from the patients' antiepileptic treatment. Most patients received polytherapy with different therapeutic mechanisms. Epileptic seizures themselves result in neurogenic inflammation and elevated IL levels. Also, the length and severity of an epileptic seizure have a considerable effect on the neurogenic inflammation that results from the seizure. In most studies, blood samples obtained during or shortly after epileptic seizures were used for analysis.[8,12] Due to this, it was discovered that epileptic patients had greater levels of IL-1 and IL-6 than controls. Since the current study was planned to exclude the effect of length and severity of the seizures on IL levels, it collected blood samples from all patients in the interictal period — at least a month after the previous seizure.

Previous studies documented anatomic asymmetry of the brain, with the left hemisphere maturing later than the right in patients with temporal epilepsy.[13] The gyrus and sulcus of the brain usually develop earlier in the right hemisphere of the embryonic brain than in the left.[14] It is thought that since the right hemisphere is fully developed 7-10 days earlier than the left, it has a protective privilege.[15] This makes the left hemisphere vulnerable to harmful events over a longer period, making it more susceptible in the long run. In other words, the left hemisphere may be significantly more prone to injury than the right hemisphere.[15]

Several studies have noted not only the presence of anatomical asymmetry in various species but also the presence of functional asymmetry.[16] EEG-based studies showed that lateralized epileptic-form discharges are more prevalent in the left hemisphere, making it more likely to develop seizures than in the right hemisphere.[17,18] Many other diseases, such as schizophrenia, depression, Alzheimer's disease, non-lacunar cerebrovascular ischaemic events, and cerebral palsy (CP), have all been associated with left hemisphere dysfunction.[15,19-24] In the current study as well, the number of individuals with epileptic seizures originating in the left hemisphere was significantly higher than those lateralized to the right hemisphere.

Apart from the anatomical differences, animal studies have shown that the right neocortex releases more ILs than the left neocortex.[6] In the current study, the levels of both ILs did not significantly differ between right and left lateralization of epilepsy patients. The lack of significant difference between hemispheres was assumed to be because the number of right-lateralized temporal epilepsy patients was significantly lower than that of left-lateralized individuals.

In the current study, IL-1 levels correlated with IL-6 levels in all epilepsy patients, regardless of epileptic hemispheric lateralization. The correlation between epilepsy duration, epilepsy onset age, or the presence of perinatal risk and IL-1 levels in all epilepsy patients demonstrated its relevance in the physiopathology of focal epilepsies. In the present study, the longer the disease duration in all epilepsy patients, the lower the IL-1 level. The longer disease duration meant longer antiepileptic medication used, which causes the suppression of IL-1 level. Also, the shorter duration of antiepileptic drug use may explain why IL-1 levels were higher in all epilepsy patients who had older onset age of epilepsy.

In terms of the relationship between IL levels with clinical and demographic data according to the lateralized temporal epileptic hemisphere, the current study found a correlation between the duration of epilepsy, epilepsy onset age, or the presence of prenatal risk and IL-1 levels in left-lateralized temporal epilepsy patients. This suggested that the left hemisphere was more susceptible to epilepsy development. In the context of ILs, IL antagonists can be used to suppress seizures in refractory epilepsy.[7,25]

The current study shed light on the involvement of IL-1 and IL-6 in the development and treatment of temporal epilepsies. The study had its limitations, as the sample size was not calculated and was small and it did not include patients who were not taking medication. Evaluation of IL levels in the interictal period and immediately after seizures could have provided more relevant information. Further research is required to fully understand how the hemispheres contribute to the development of epilepsy.

Conclusion

IL-1 and IL-6 were found to have the potential to be important in developing temporal epilepsies. The number of patients with left-lateralized temporal epilepsy was higher than with right-lateralized temporal epilepsy, and there was a link between IL-1 levels and epilepsy duration, age at onset, or prenatal risk in individuals with left-lateralized temporal epilepsy.

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Author Contribution:

AOV: Concept, design, writing, reviewing, literature, final approval.
AA: Concept, design, data analysis, final approval.
HK: Concept, design, evaluated the statistically, final approval.
HE: Concept, design, data analysis and interpretation, final approval.