Original Article

DOI: 10.4274/haseki.galenos.2025.07269
Med Bull Haseki 2025;63(4):195-201

Serum Interleukin-6 as a Potential Biomarker in Absence Epilepsy

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Abstract

Aim: The role of inflammation in absence epilepsy remains a subject of debate. The present study aims to assess the role of interleukin-6 (IL-6) in absence epilepsy by determining serum IL-6 levels of children with absence epilepsy and the association with anti-seizure medications, seizure frequency, and semiology by comparing to a control group.

Methods: Fifteen children aged 3-17 years who were followed up with the diagnosis of absence epilepsy and 30 healthy controls were included in this cross-sectional observational study between November 2020 and April 2021. Serum IL-6 levels of subjects were measured by the chemiluminescence method.

Results: Serum IL-6 levels in the patient group were significantly lower (2.98±1.02 pg/mL) than in the controls (5.35±0.87 pg/mL) ($p<0.001$). The patients receiving valproic acid monotherapy had significantly lower serum IL-6 levels than both the patients receiving other anti-seizure medications and healthy controls ($p=0.04$). Patients with active seizures had higher serum IL-6 levels than seizure-free patients (3.52±0.54 pg/mL, 2.72±1.12 pg/mL; $p=0.01$, respectively). Moreover, there was a moderate to strong positive correlation between the presence of active seizures and serum IL-6 levels (Spearman's $p=0.629$, $p=0.0069$).

Conclusion: Our study is the first clinical investigation of IL-6 concentrations in absence epilepsy patients and possible relations between IL-6 and patient characteristics.

Keywords: Absence, epilepsy, interleukin-6, seizures, valproic acid

Introduction

The role of immunity in epilepsy was first proposed in the 1960s (1). Today, an increasing amount of evidence from both preclinical animal models and human studies indicates that brain inflammation is associated with epilepsy (2). Besides, it remains uncertain whether the inflammatory alterations in the central nervous system (CNS) contribute to epileptogenesis, or these alterations occur as a consequence of epileptic activity.

Cytokines, which are soluble signaling peptides secreted by numerous cell types including macrophages (e.g., microglia), T and B lymphocytes, mast cells, endothelial cells, and fibroblasts, play a crucial role in not only the proper function and development of CNS, but also in CNS disorders (3). In previous studies, it has been demonstrated that cytokines, including interleukin (IL)-1β, IL-6, tumor necrosis factor-α (TNF-α), and IL-8 may enhance the permeability of the blood-brain barrier (BBB) (4). Leakage through the BBB is thought to induce

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Received: 03.08.2025 **Accepted:** 22.09.2025 **Publication Date:** 02.10.2025

***The results were previously presented at the 14th European Paediatric Neurology Society Congress (28th April-2nd May 2022, Glasgow, United Kingdom). Available in the online abstract book (page 222): https://www.epns.info/wp-content/uploads/2022/05/EPNS22_Abstract_PDF.pdf**

Cite this article as: Basarir G, Baysoy A, Bozkaya Yilmaz S, Colak A, Olgac Dundar N, Gencpinar P. Serum interleukin-6 as a potential biomarker in absence epilepsy. Med Bull Haseki. 2025;63(4):195-201

seizures and lead to progression of epileptogenesis (4). Moreover, pro-inflammatory cytokines, notably IL-6, can increase the extracellular glutamate level that results in glutamate neurotoxicity and excitatory transmission in the brain (5). Neurotoxic effects of IL-6 are also associated with suppression of γ-aminobutyric acid (GABA)-ergic inhibition via endocytosis of $GABA_A$ receptors (5). Recent studies with epilepsy patients have addressed the function of IL-6 in both peri-ictal and chronic neuroinflammation. Serum and cerebrospinal fluid concentrations of IL-6, as a pleiotropic cytokine, have been reported to fluctuate in both ictal and interictal periods in patients with epilepsy (6). Elevated IL-6 levels were mostly associated with generalized tonic-clonic seizures, refractory seizures, or temporal lobe epilepsy (TLE) in previous studies (7). Absence epilepsy (AE) is characterized predominantly by non-motor seizures that cause a brief loss of awareness of abrupt onset and offset with generalized 3 Hz spike-and-wave discharges (SWDs) electrographically (8). Both childhood and juvenile forms of AE are polygenic syndromes involving the genes that encode GABA receptors, T-type calcium channels, and glucose transporter type 1 (9). However, the role of inflammation in the modulation of AE is still unclear. In some animal models, administration of bacterial endotoxin lipopolysaccharide (LPS) has been shown to increase cytokine levels, including IL-6, and enhance SWDs and absence seizures (10).

Despite the supportive results of animal studies, there are no data about the levels of IL-6 in children with AE. To address this issue, we investigated serum IL-6 concentrations of children with AE and their association with anti-seizure medications (ASMs), seizure semiology, and frequency of seizures by comparing them with control subjects. Through investigating the association between IL-6 and AE, we also suggest a possible role for immunomodulatory therapies in future clinical management.

Materials and Methods

Compliance with Ethical Standards

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and approved by the University of Health Sciences Türkiye, Izmir Tepecik Training and Research Hospital Clinical Research Ethical Committee (approval no.: 01 date: 08.10.2020). Written informed consent was obtained from the children and/or children's parents or legal guardians following a detailed explanation.

Study Design

This is a cross-sectional observational case-control study conducted on fifteen children aged 3 to 17 years with a diagnosis of AE in the pediatric neurology outpatient clinics and 30 healthy controls between November 2020 and April 2021. Patients' clinical data were evaluated and those meeting the following criteria were included: Patients followed for at least six months with a clinical diagnosis of AE based on seizure semiology and electroencephalogram (EEG) findings, according to the criteria of the International League of Epilepsy (ILAE) current guidelines (8). The exclusion criteria consisted of having an immunologic disease or an acute/chronic infectious disease and receiving an immune-related treatment in the last six months. A detailed neurological examination, an EEG record according to the 10-20 international system of electrode placement, and a brain magnetic resonance imaging (MRI) were performed on all the patients. A flow diagram illustrating the enrollment of patients, application of exclusion criteria, and final study groups is presented in Figure 1.

Measurement of serum IL-6 levels: samples from participants were collected in a clot-activating tube containing a gel separator (BD Vacutainer® SST II Advance tube, 5 mL, 13 x 100 mm, NJ, USA). Each tube was centrifuged at 1500 × g for 10 minutes. The samples were stored at -80 °C. Serum IL-6 concentrations were measured by the chemiluminescence method using the Immulite 2000 autoanalyzer (Siemens Healthcare Diagnostics, Marburg, Germany).

Statistical Analysis

Data were analyzed using the SPSS software (Statistical Package for Social Science), version 29. Percentage and frequency (n) were calculated for the categorical data, whereas mean and standard deviation values were calculated for the continuous variables. The normality of data distribution was assessed using the Shapiro-Wilk test. For group comparisons, the chi-square test was applied to categorical variables, Student's t-test was used for normally distributed continuous variables, and the Mann-Whitney U test was applied for non-normally distributed continuous variables. P-values of less than 0.05 were considered to be significant.

Results

The study was conducted on a patient group consisting of fifteen children (8 girls and 7 boys) with AE and a control group consisting of 30 healthy subjects (16 girls and 14 boys). Demographic characteristics and IL-6 levels of the patients and the control group were summarized in Table 1. Serum IL-6 levels in the patient group were significantly lower (2.98±1.02) than in the control group (5.35±0.87) ($p<0.001$).

Among the patient group, ten patients were receiving valproic acid (VPA) monotherapy; one patient was receiving ethosuximide (ETH) monotherapy; one patient was receiving oxcarbazepine (OXC) and lamotrigine

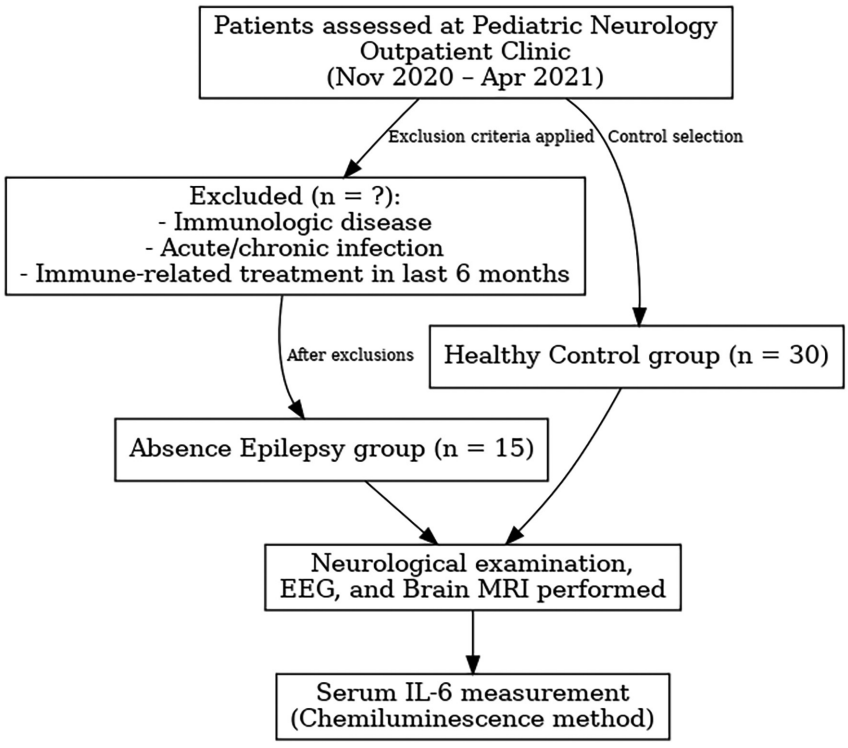

Figure 1. Flow diagram of the study
IL: Interleukin, MRI: Magnetic resonance imaging

Table 1. Demographic characteristics and IL-6 levels of the study population

		Patient group (n=15)	Control group (n=30)	p
Age (year)	Mean ± SD	10.5±3.6	11.2±3.8	0.46[a]
	Range	3-16	3-17	
Male/Female	Male (%)	7 (46.7)	14 (46.7)	1.00[b]
	Female (%)	8 (53.3)	16 (53.3)	
IL-6 (pg/mL)	Mean ± SD	2.98±1.02	5.35±0.87	**<0.001**[a]
	Range	2.08-5.81	3.5-6.78	

[a]:Mann-Whitney U test was used. [b]:Chi-square test was used, p-values <0.05 are shown in bold
IL: Interleukin, n: Number, SD: Standard deviation, pg/mL: Picogram/milliliters

(LTG); one patient was receiving ETH, VPA, LTG and clobazam; one patient was receiving levetiracetam (LEV) and topiramate (TPR); and one patient was receiving ETH, VPA, and LEV. The patients receiving only VPA treatment had significantly lower serum IL-6 values when compared to the patients receiving other ASMs or polytherapy for treatment (p=0.04). Twelve patients had normal brain MRI findings, whereas one of the patients had mild cerebellar atrophy. All the patients had generalized 3 Hz SWDs on EEG before anti-seizure treatment. However, EEG records of nine patients were normal under the anti-seizure treatment during the period of sample collection, while six patients still had SWDs on EEG. Brain MRI and EEG findings had no effect on serum IL-6 levels of the patients (p=0.57, p=0.14, respectively). We found a moderate-to-strong positive correlation between the presence of active seizures and serum IL-6 levels (Spearman's p=0.629, p=0.0069). Assessment of serum IL-6 levels according to seizure types, seizure control, brain MRI and EEG findings, and ASMs received is given in Table 2.

Discussion

Patients with AE had significantly reduced serum IL-6 concentrations compared to sex- and age-matched healthy controls in our study. (p<0.001). This finding suggests that AE may be characterized by a distinct immune profile compared with some other epilepsy syndromes in which elevated IL-6 levels have frequently been reported. One

Table 2. Assessment of serum IL-6 concentrations according to the patient characteristics				
		n	IL-6 (pg/mL) Mean ± SD	p
Type of seizures	Absence	12	2.96±1.09	0.54[a]
	Absence and GTCs	3	3.08±0.95	
Seizure control	Seizure-free	10	2.72±1.12	**0.01**[a]
	Non-seizure free	5	3.52±0.54	
Brain MRI findings	Normal	12	3.02±1.06	0.61[a]
	Abnormal	1	2.24	
EEG findings	Normal	9	2.89±1.26	0.14[a]
	Abnormal	6	3.12±0.6	
Anti-seizure medication	VPA monotherapy	10	2.55±0.51	**0.04**[a]
	Other ASMs/Polytherapy	5	3.86±1.28	

[a]:Mann-Whitney U test was used, p values <0.05 are shown in bold
ASM: Anti-seizure medication, EEG: Electroencephalography, GTCs: Generalized tonic-clonic seizures, IL: Interleukin, MRI: Magnetic resonance imaging, n: Number, pg/mL: Picogram/milliliters, SD: Standard deviation, VPA: Valproic acid

potential explanation for this phenomenon is that reduced IL-6 levels reflect a compensatory mechanism aimed at limiting chronic neuroinflammation in AE. Alternatively, the reduced IL-6 levels observed in our cohort may at least partly be attributable to the widespread use of VPA, which has been shown to suppress cytokine production through nuclear factor kappa B (NF-κB) inhibition (11). At present, there is a lack of data about the role of cytokines in AE. Despite the existence of numerous clinical studies examining the function of various cytokines in other forms of epilepsy, there is a paucity of research that focuses on the potential role of cytokines in the epileptogenesis of AE patients. Moreover, the results of clinical studies on patients with other epilepsies are conflicting. Similar to our results, Alvim et al. (12) recently showed that several plasma cytokine levels, including IL-6, are lower in the patient group independent of the underlying etiology in a cohort study with 446 epilepsy patients and 166 healthy controls. In contrast, a previous meta-analysis of 66 studies involving 1934 patients reported elevated serum IL-6 levels in epilepsy patients with several etiologies, including TLE, West syndrome, and refractory epilepsy, as well as in acute seizures (7). A recent study has demonstrated that interictal elevations of IL-6 and TNF-α are associated with an increased risk of seizure recurrence (13). Furthermore, the study found a negative correlation between IL-6 levels and time to seizure recurrence (13).

Despite the much evidence supporting the crucial role of inflammatory cytokines in both the course and pathogenesis of epilepsy, the exact mechanism remains unclear. Most studies have focused on pro-inflammatory cytokines involving IL-1β, TNF-α, and IL-6. Epileptic seizures have been shown to not only affect the expression of these pro-inflammatory cytokines in the brain but also alter their serum concentrations (14-16). A recent Mendelian randomization analysis revealed that genetically simulating IL-6R blockade was associated with a modest but significant reduction in overall epilepsy risk [odds ratio (OR) 0.827, 95% confidence interval (CI) 0.685-1.000, p=0.05], suggesting a tentative causal role for IL-6 signaling in epileptogenesis (17). Although their study supports our results and suggests IL-6R inhibition as a potential therapeutic strategy in epilepsy, the subtype analysis demonstrated that the effect of IL-6R blockade was not statistically significant in AE (17).

Almost all of the existing data on the role of cytokines in AE come from animal studies. A previous study with the Wistar Albino Glaxo/Rijswijk (WAG/Rij) strain, an animal model of AE, showed that an increase in thalamic NF-κB and IL-6 levels results in a decrease in the SWDs and seizure activity (18). Another study with WAG/Rij rats showed that rapamycin treatment (a specific mechanistic target of rapamycin inhibitor) decreases the development of absence seizures and provides about a 52% reduction of SWDs by preventing the release of inflammatory cytokines (19). Leo et al. (20) demonstrated that administration of tocilizumab, a monoclonal antibody against the IL-6 receptor, resulted in a substantial decrease in absence seizures in the WAG/Rij rats with AE. In line with our findings suggesting an immunological component in AE, a very recent experimental study demonstrated that long-term treatment with low doses of edaravone, a free radical scavenger, reduced the incidence of SWDs in WAG/Rij rats by attenuating oxidative stress and neuroinflammation (21). Accumulating experimental evidence from animal studies leads us to speculate about alterations in the serum IL-6 concentrations of AE patients.

Furthermore, we detected elevated serum IL-6 levels in patients with uncontrolled seizures compared to seizure-free patients (p=0.01). A moderate-to-strong positive

correlation was identified between the existence of active seizures and serum IL-6 levels (Spearman's p=0.629, p=0.0069), indicating that patients with ongoing seizures tend to have higher IL-6 levels. These results indicate significant clinical implications, namely that serum IL-6 levels may serve as a reliable indicator of seizure activity in patients with AE. Previous studies comparing the interictal and postictal serum IL-6 levels in patients with active seizures have conflicting results (22-25). A previous study comparing patients with refractory and well-controlled epilepsy indicated that serum IL-6 and oxidative stress markers were significantly higher in refractory epilepsy patients than in well-controlled epilepsy patients (26). In a previous study, Alapirtti et al. (23) revealed that IL-6 concentrations remained unchanged following a single seizure in patients with frequent seizures, whereas increased IL-6 concentrations were detected in patients with infrequent seizures. Moreover, they emphasized that the patients with frequent seizures had chronically elevated IL-6 levels, whereas baseline IL-6 concentrations were reduced in patients with infrequent seizures (23).

Another factor altering the serum cytokine concentrations in epilepsy patients is the modulatory effect of ASMs on the immune system. Our study indicated that the patients receiving VPA monotherapy had significantly reduced serum IL-6 concentrations compared to both the patients receiving other ASMs and healthy controls (p=0.04). These results underscore the immunomodulatory properties of VPA, which extend beyond the realm of seizure suppression. Steinborn et al. (27) revealed a significant decrease in serum IL-6 levels following a period of four to six months of VPA treatment in patients with generalized epilepsy (p<0.001). A previous in vitro study also demonstrated the production of both TNF-α and IL-6 to be inhibited by VPA through the suppression of NF-κB activation (11). A more recent study showed that VPA combined with LEV lowers the serum IL-6 levels and improves the EEG findings in pediatric epilepsy patients (28). In contrast, another study comparing patients receiving VPA or LEV treatment found that both ASMs have no effect on interictal serum levels of IL-1β, IL-6, and TNF-α (29). Abu-Rish et al. (30) showed that LTG significantly inhibits IL-1β, IL-6, and TNF-α excretion in vivo and in vitro, specifically in LPS-treated RAW264.7 cells. The reducing effect of TPR on the LPS-activated excretion of these three cytokines has also been shown in rat cortical microglial cells (31). However, in a study of patients with focal and generalized epilepsy, no significant alteration was detected in serum concentrations of these cytokines after 12 months of TPR or VPA treatment (32). Another study demonstrated that six months of OXC therapy resulted in a significant decrease in IL-2, TNF-α, and IL-6 concentrations (33). Carbamazepine has been shown to elevate serum IL-1α, IL-1β, IL-2, and IL-6 levels after 1 year of therapy (34).

Normal EEG findings did not affect the patients in our study. Unlike our results, a previous study demonstrated that decreased serum IL-6 levels were accompanied by improvement in EEG patterns in patients with electrical status epilepticus in sleep (35). Another study of 75 children with idiopathic epilepsy indicated that serum concentrations of IL-2, TNF-α, and IL-6 in epilepsy patients with epileptic discharges and slow waves on EEG were significantly higher than those with normal EEG (36).

Study Limitations

Our study presents several limitations. The results must be interpreted with caution due to the relatively small number of patients and the heterogeneity of patient characteristics such as ASM dosage and duration of drug treatment. An important limitation of our study is that we studied only one type of serum cytokine level. Despite these limitations, the main strength of this study is that it represents the first clinical investigation specifically evaluating serum IL-6 levels in children with AE. The inclusion of a well-defined patient group diagnosed according to standardized ILAE criteria and age- and sex-matched healthy controls enhances both the validity and the clinical relevance of the findings. Moreover, by highlighting a potential immunological mechanism, this study provides a basis for larger cohorts.

Conclusion

Although evidence from other epilepsy syndromes is conflicting, our data provide the first direct clinical evidence that serum IL-6 is altered in AE and related to both seizure control and ASM type. This adds a novel dimension to the understanding of AE pathogenesis, suggesting that immune mechanisms may play a role. Notably, serum IL-6 concentrations were significantly lower in patients with AE receiving VPA monotherapy than in patients receiving other ASMs or healthy controls, supporting the immunomodulatory effect of VPA. Taken together, our findings indicate that IL-6 may serve as a biomarker reflecting disease activity and treatment response in AE. To our knowledge, this is the first clinical study to explore the role of the immune system in AE and to demonstrate associations between serum IL-6 concentrations and patient characteristics influencing the disease course. Future studies with larger cohorts and longitudinal designs are needed to validate these results and to further investigate the neuromodulatory role of IL-6 as a biomarker in AE.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the ethical principles

stated in the Declaration of Helsinki and approved by the University of Health Sciences Türkiye, Izmir Tepecik Training and Research Hospital Clinical Research Ethical Committee (approval no.: 01 date: 08.10.2020).

Informed Consent: Written informed consent was obtained from the children and/or children's parents or legal guardians following a detailed explanation.

Acknowledgments

We thank colleagues of the hospital authority and department of medical biochemistry for facilitating this study.

Footnotes

Authorship Contributions

Concept: G.B., A.B., S.B.Y., A.C., N.O.D., P.G., Design: G.B., A.B., S.B.Y., A.C., N.O.D., P.G., Data Collection or Processing: G.B., A.B., S.B.Y., Analysis or Interpretation: A.C., N.O.D., P.G., Literature Search: G.B., A.C., N.O.D., P.G., Writing: G.B.

Conflict of Interest: No conflicts of interest were declared by the authors.

Financial Disclosure: This study received no financial support.

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