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Interleukin-6, interleukin-1 beta and interleukin-1 receptor antagonist levels in epileptic seizures

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ABSTRACT

Purpose: Data are accumulating to support the involvement of inflammatory mechanisms in the pathogenesis and course of epilepsy.
Methods: The aim of this study was to examine seizure-induced changes in plasma concentrations of interleukin-6 (IL-6), interleukin-1 receptor antagonist (IL-1Ra), and interleukin-1 beta (IL-1β) in 23 patients with epilepsy undergoing a video-electroencephalography (EEG) study. Patients were divided into groups based on epilepsy type as follows: temporal lobe epilepsy (TLE) ($n = 6$), extra-temporal lobe epilepsy (XLE) ($n = 8$) and idiopathic generalised epilepsy (IGE) ($n = 9$). Serum levels of IL-1β, IL-1Ra and IL-6 were measured at baseline, immediately after the epileptic seizure, and at 3 h, 6 h, 12 h and 24 h after the seizure.
Results: We demonstrated a significant increase in plasma levels of IL-6 and IL-1Ra that peaked at 12 h into the post-ictal period ($p < 0.05$). IL-1β levels did not differ from the baseline levels. We did not observe any differences in post-ictal cytokine release patterns between the TLE, XLE and IGE groups.
Conclusion: The present study confirms the findings that epileptic seizures induce the production of IL-6 and IL-1Ra.

1. Introduction

Cytokines are a heterogeneous group of polypeptide compounds that act principally as mediators of inflammatory signals in peripheral tissues.[1] In experimental models, an increased production of inflammatory cytokines in association with epileptic seizures has been demonstrated. The cytokines interleukin-1 (IL-1) and interleukin-6 (IL-6) receive much attention in this regard.

The IL-1 cytokine family consists of IL-1 alpha, IL-1 beta (IL-1β) and IL-1 receptor antagonist (IL-1Ra).[2] Neurological conditions such as stroke,[3] trauma[4] and Alzheimer's disease[5] are associated with increased IL-1β production in the CNS. In low concentrations, IL-1β is neuro-protective, but in pathological circumstances, high levels of IL-1β lead to neurotoxic effects. Thus, it is associated with seizure susceptibility and epileptogenesis.[6] Increased mRNA levels of IL-1β and IL-1Ra have been observed in experimentally induced seizures.[7–10] However, in most clinical studies, IL-1β levels remained unchanged during the post-ictal period, and the reports regarding seizure-induced changes in IL-1Ra levels have been contradictory.[11–13]

IL-6 is a pleiotropic cytokine with a spectrum of biologic actions on various cell types and tissues.[14] The expression of IL-6 is increased in the setting of various neurological disorders such as multiple sclerosis,[15] Alzheimer's disease,[16] trauma[17] and meningitis.[18] In transgenic mice that are over-expressing IL-6, neurologic impairment is observed.[19] Conversely, neuro-protective effects of IL-6 are demonstrated in rat brain cultures.[20,21] Increased IL-6 levels after both focal and secondarily generalised epileptic seizures have been observed in clinical studies.[13,22–24,16]

The role of specific brain regions in controlling cytokine responses and the significance of seizure and epilepsy types for the epilepsy-related immune responses are less well defined.

In this study, we aimed to investigate changes in IL-6, IL-1β and IL-1Ra levels triggered by epileptic seizures, as well as the time interval and the relation of these changes with the type of epilepsy. We recruited patients with epilepsy who were undergoing a video-EEG study, which is a methodology that allowed us to accurately diagnose and classify epileptic seizures and to assess their temporal relationship with cytokine levels.

2. Methods

We studied consecutive patients who were admitted to the video-EEG monitoring unit for pre-surgical epilepsy evaluation. The Ethics Committee of the hospital approved the study, and all

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the patients gave written informed consent. The inclusion criterion was at least a 5-year history of epilepsy. Patients with seizures within the last 24 h, trauma within the last 2 weeks, electrolyte disturbances, history of alcohol or drug withdrawal, acute neurological diseases, inflammatory, autoimmune, metabolic or neoplastic diseases and patients using any other drugs other than anti-epileptic medication were excluded. The study group consisted of 18 men and 5 women. The mean age in the study group was 27.74 ± 8.91 years (range 15–46).

All patients underwent five days of video-EEG monitoring while continuing anti-convulsant medications. Video-EEG monitoring was performed using 21 scalp electrodes, which were placed according to the International 10–20 System.

All seizures were characterised as single non-prolonged seizures. The patients experienced no further seizures within 24 h after the index seizure.

TLE, XLE and IGE were diagnosed based on medical history, electro-clinical findings (seizure semiology and EEG/video-EEG) and neuro-imaging.[12] A high-resolution 1.5 Tesla magnetic resonance imaging (MRI) scan of the brain with a specific epilepsy protocol was obtained to define the aetiology and was classified as follows: normal, hippocampal sclerosis and other causes of epilepsy such as chronic lesions of trauma, central nervous system infection or stroke. Plasma samples were collected at 08.00 a.m. at the beginning of the five-day recordings (baseline values) as soon as possible after the first seizure (0 h) and at 3, 6, 12 and 24 h after the index seizure. The serum samples were immediately centrifuged and frozen at −80 °C until further processing.

IL-6, IL-1Ra and IL-1β were measured by commercially available ELISA (Enzyme Linked Immunosorbent Assay) kits (Human IL-6 High Sensitivity ELISA, Bender MedSystems GmbH, Austria; Human IL-1Ra Cytoscreen ELISA, Biosource, Belgium and Human IL-1β Platinum ELISA, Bender MedSystems GmbH, Austria) according to the manufacturers' instructions.

We investigated significant changes in serum cytokine levels immediately after and at 3, 6, 12 and 24 h after the epileptic seizure in the TLE, XLE and IGE groups.

Statistical calculations were carried out using Statistical Package for the Social Sciences (SPSS) 13.00. The *t*-test was used to compare baseline cytokine levels to the normal concentrations of IL-1β, IL-1Ra and IL-6. Friedman analysis of variance (ANOVA) with post- hoc comparisons (Wilcoxon matched pairs test) and the Mann–Whitney *U*-test were used to compare cytokine levels at different time points. Correlations were calculated using Pearson and Spearman correlation analyses. Findings were considered statistically significant at p values less than 0.05.

Table 2
High and low baseline cytokine levels.

	TLE	XLE	IGE	Total
IL-6 > 1.5 pg/ml (%)	4/6 (66.7)	2/8 (25)	4/9 (44.4)	10 (43.5)
IL-1β > 0.3 pg/ml (%)	5/6 (83.3)	6/8 (75)	8/9 (88.9)	19 (82.6)
IL-1Ra < 0.2 ng/ml (%)	5/6 (83.3)	8/8 (100)	8/9 (88.9)	21 (91.3)

3. Results

The clinical characteristics of the patients are presented in Table 1. The mean seizure frequency was 13 ± 16.27 seizures per month. The prominent seizure types were generalised tonic–clonic seizures in IGE, secondary generalised tonic–clonic seizures in patients with XLE and complex partial seizures in patients with TLE. All patients in the IGE group had normal brain MRI. Hippocampal sclerosis was observed in only one TLE patient. Chronic lesions of trauma, encephalitis and brain infarction were observed in XLE patients and were categorised as causes of epilepsy other than hippocampal sclerosis (Table 1).

Baseline IL-1β levels were significantly higher, and baseline IL-1Ra levels were significantly lower than in the normal population ($p < 0.01$) (normal concentrations: 0.3 pg/ml for IL-1β and 0.2 ng/ml for IL-1Ra).[25,26] While the TLE group did not differ from the normal population, then XLE and IGE groups showed lower IL-1Ra (both $p < 0.01$) and higher IL-1β ($p = 0.02$ and $p = 0.04$ respectively) levels than the normal population. Our patients' baseline IL-6 levels were not different than those in the normal population (normal concentration: 1.5 pg/ml)[26] (Table 2).

Baseline cytokine levels were not correlated with the frequency of seizures.

We observed a significant increase in IL-6 and IL-1Ra in the 12-h post-ictal period compared to the baseline measures. No significant post-ictal changes were observed for IL-1β (Tables 3–5, Figs. 1 and 2).

The IL-1β/IL-1Ra ratio decreased significantly three hours after the epileptic seizure ($p = 0.03$) (Table 6).

No significant correlations of epilepsy syndrome with post-ictal changes in the concentrations of IL-6, IL-1Ra, IL-1β or IL1β/IL-1Ra were noted.

Table 1
Clinical characteristic of patients.

Epilepsy syndrome	TLE	XLE	IGE	Total
n	6	8	9	23
Female/male	1/5	2/6	2/7	5/18
Age (mean ± SD years)	31 ± 10.51 (17–43)	23.38 ± 6.59 (16–35)	29.44 ± 9.02 (15–46)	27.74 ± 8.91 (15–46)
Epilepsy duration (mean ± SD years)	17.83 ± 9.75 (3–33)	6.87 ± 4.94 (1–13)	16.55 ± 8.26 (8–37)	13.52 ± 8.89 (1–37)
Seizure frequency (mean ± SD seizure/month)	13 ± 18.4 (2–50)	18.75 ± 20.58 (3–60)	7.92 ± 9.15 (0.3–30)	13 ± 16.27 (0.3–60)
Recorded index seizure type	4 CPS, 2 SGTCS	2 CPS, 6 SGTCS	9 GTCS	6 CPS, 8 SGTCS, 9 GTCS
Brain MRI (*n*, %)				
Normal	5 (83.3)	5 (62.5)	9 (100)	19 (82.6)
Hippocampal sclerosis	1 (16.7)	–	–	1(4.3)
Other causes	–	3 (37.5)	–	3 (13)
Side of epilepsy (*n*, %)				
Right	2 (33.3)	1 (12.5)	2 (22.2)	5 (21.7)
Left	0	2 (25)	3 (33.3)	5 (21.7)
Unidentified	4 (66.7)	5 (62.5)	4 (44.4)	13 (56.5)
Anti-epileptic drugs (*n*, %)				
Without therapy	0	1 (12.5)	0	1 (4.3)
Mono-therapy	0	1 (12.5)	3 (33.3)	4 (17.4)
Bi-therapy	2 (33.3)	2 (25)	3 (33.3)	7 (30.4)
Poly-therapy	4 (66.7)	4 (50)	3 (33.3)	11 (47.8)
Refractory drug epilepsy (*n*, %) (>2 seizures/month during last year)	4 (66.7)	8 (100)	7 (77.8)	19 (82.6)

Table 3
Circulating concentrations of IL-6.

Epilepsy syndrome	Baseline	0 h	3 h	6 h	12 h	24 h
TLE	4.44 ± 5.29 (0.14–14.18)	1.04 ± 0.86 (0.33–2.64)	2.3 ± 3.5 (0.33–9.28)	5.23 ± 6.63 (0.29–16.3)	10 ± 8.78 (0.14–24.88)	3.24 ± 4.8 (0.12–12.79)
XLE	3.05 ± 6.12 (0.16–17.76)	1.13 ± 0.88 (0.23–2.58)	1.87 ± 2.29 (0.34–6.75)	1.55 ± 2.15 (0.01–6.28)	7.51 ± 11.14 (0.02–29.2)	3.28 ± 4.94 (0.01–12.44)
IGE	1.33 ± 1.29 (0.01–3.86)	4.3 ± 9.54 (0.09–29.47)	1.95 ± 2.68 (0.03–7.78)	12.31 ± 20.88 (0.15–51.08)	5.37 ± 6.26 (0.52–17.69)	8.91 ± 11.92 (0.13–27.86)
Total	2.74 ± 4.53 (0.01–17.76)	2.35 ± 6 (0.09–29.47)	2.01 ± 2.66 (0.03–9.28)	6.72 ± 13.90 (0.01–51.08)	*7.32 ± 8.65 (0.02–29.2)	5.47 ± 8.52 (0.01–27.86)

Baseline: before the seizure; 0 h: immediate post-ictal state. Values in pg/ml, mean ± SD.
* 12 h > baseline ($p = 0.039$).

Table 4
Circulating concentrations of IL-1Ra.

	Baseline	0 h	3 h	6 h	12 h	24 h
TLE	99.12 ± 104.32 (11.4–305.2)	124.8 ± 129.78 (30.6–385.2)	127.38 ± 106.81 (65–343.3)	174.95 ± 177.19 (72.5–528.6)	172.98 ± 119.32 (89.9–406)	154.83 ± 119.56 (59.2–384.8)
XLE	78.18 ± 21.64 (46.4–117.1)	80.23 ± 15.5 (51.4–97)	89.26 ± 23.68 (52.6–129.6)	78.54 ± 13.63 (59.6–97)	98.81 ± 39.28 (58.4–169.5)	76.09 ± 14.45 (53–95.8)
IGE	170.52 ± 227.17 (48.7–772.4)	204.43 ± 263.75 (55.7–882.7)	190.5 ± 233.47 (65.4–760.7)	186.8 ± 247.73 (53–828.1)	191.73 ± 264.39 (56.1–884.2)	119.18 ± 68.25 (54.5–272.9)
Total	119.77 ± 152.27 (11.4–772.4)	140.46 ± 179.62 (30.6–882.7)	138.82 ± 156.89 (52.6–760.7)	146.05 ± 179.1 (53–828.1)	*154.52 ± 175.88 (56.1–884.2)	113.49 ± 77.44 (53–384.8)

Baseline: before the seizure; 0 h: Immediate post-ictal state. Values in pg/ml, mean ± SD.
* 12 h > baseline ($p = 0.019$).

The patients with low baseline IL-1Ra and high baseline IL-1β levels showed more significant increases in IL-6 and IL-1Ra concentrations in the 12-h post-ictal period ($p = 0.024$ and 0.04 for IL-6, respectively; $p = 0.05$ and $p = 0.03$ for IL-1Ra, respectively).

Baseline cytokine levels and the post-ictal changes in cytokine levels were not influenced by the side of epilepsy, the frequency of seizures, the aetiology of the seizures or the anti-epileptic drugs.

4. Discussion

Basal IL-6 levels may be increased in patients with chronic epilepsy when compared with healthy controls.[13,27,28] In some studies, basal IL-6 has been reported to be more affected in patients with TLE than in patients with XLE.[27,28] In our patients, basal IL-6 levels did not differ from those in the normal population. A genetic predisposition to higher production of IL-1β in TLE patients with hippocampal sclerosis has been reported in Japanese patients.[29] These results were not confirmed in other case-control studies in European and Chinese populations.[30–32] TLE is the only epilepsy syndrome with sufficient data regarding the varied baseline cytokine levels. In epileptic patients, we found higher baseline levels of IL-1β and lower baseline levels of IL-1Ra than in the normal population. These changes were especially significant in the XLE group. The activity of the IL-1 system depends on the balance between agonist/antagonist ligands, IL-1β and IL-1Ra. Disequilibrium in the IL-1β/IL-1Ra ratio may increase the inflammatory and neurotoxic potential of IL-1β and lead to brain damage and epilepsy.[33] One potential explanation for the high levels of IL-1β and the low levels of IL-1Ra in our patients is a cytokine gene polymorphism resulting in impaired inflammatory responses and the development of epilepsy. The lack of significant variations in the baseline cytokine levels in the TLE group may be due to the small number of cases ($n = 6$).

The main goal of the present study was to evaluate seizure-induced changes in cytokine levels. We observed increased post-ictal IL-6 and IL-1Ra levels that peaked at 12 h in both the TLE and XLE groups. IL-1β levels remained unchanged in the TLE, XLE and IGE groups. In experimental seizure models, exogenously applied IL-1β worsens seizures, while the depression of IL-1β activity suppresses them.[10,34] The administration of exogenous IL-1Ra has anti-convulsant effects.[35] Experimental seizures are associated with post-ictal increases of IL-1β in the CNS. In clinical studies, no observable differences in IL-1β concentrations after seizures have been observed.[11–13,22] Peltola et al. compared plasma cytokine levels of patients with recent (72 h) primarily generalised or partial secondarily generalised tonic–clonic seizures to patients who suffered a seizure more than 2 weeks previously. They attributed the similar IL-1 levels to the short half-life of the cytokine.[11] In

Table 5
Circulating concentrations of IL-1β.

	Baseline	0 h	3 h	6 h	12 h	24 h
TLE	1.07 ± 0.85 (0.08–2.24)	1.25 ± 1.03 (0.08–2.78)	1.43 ± 0.95 (0.35–2.51)	1.07 ± 1.09 (0.08–2.51)	1.12 ± 1.31 (0.08–3.59)	1.03 ± 0.44 (0.35–1.7)
XLE	2.21 ± 1.84 (0.08–5.21)	2.21 ± 1.66 (0.62–5.75)	1.97 ± 1.54 (0.08–3.86)	2.07 ± 1.51 (0.08–3.86)	2.81 ± 2.27 (0.08–6.83)	2.38 ± 1.75 (0.35–5.48)
IGE	1.7 ± 1.71 (0.07–5.48)	2.57 ± 2.12 (0.08–7.1)	1.07 ± 1.2 (0.08–3.86)	3.11 ± 4.26 (0.08–13.04)	1.79 ± 1.58 (0.07–4.4)	9.07 ± 19.94 (0.08–61.9)
Total	1.71 ± 1.58 (0.07–5.48)	2.1 ± 1.75 (0.08–7.1)	1.48 ± 1.28 (0.08–3.86)	2.22 ± 2.88 (0.08–13.04)	1.97 ± 1.84 (0.07–6.83)	4.64 ± 12.61 (0.08–61.9)

Baseline: before the seizure; 0 h: Immediate post-ictal state. Values in pg/ml, mean ± SD.

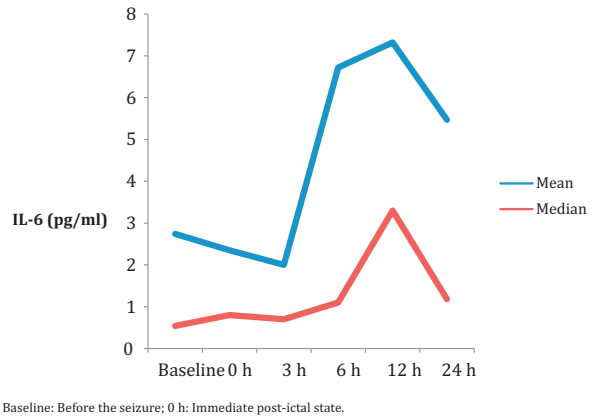

Fig. 1. Mean and median IL-6 concentrations of the patients before and after the index seizure.

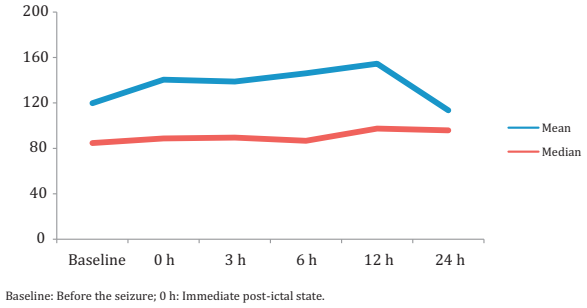

Fig. 2. Mean and median IL-1Ra concentrations of the patients before and after the index seizure.

2000, they analysed IL-1β and IL-Ra levels within 24 h of a seizure in patients with newly developed tonic–clonic seizures, and they compared these levels to those of controls. They showed a small effect on IL-Ra concentrations, but even with this short sample collection time, they could not show any changes in IL-1β levels.[12] In a video-EEG study, Alapirtti et al. reported that post-ictal plasma levels of IL-1Ra and IL-1β did not significantly differ from baseline levels in either the TLE or XLE groups.[22] They suggested that the augmentation in IL-1Ra, which is mainly induced by IL-1β, might reflect the activation of the IL-1 system. The results of the study of Lehtimäki et al. were similar and showed constant levels of IL-1β, but there was an increase in IL-1Ra levels.[13] The failure to show any increase in IL-1β levels in these studies is thought to be caused by the local production of the cytokine in very low quantities.[36] Our study results are in agreement with existing data on elevated IL-1Ra and steady IL-1β serum concentrations after the epileptic seizures. To better understand the status of the IL-1 system, we analysed the changes in the IL-1β/IL-1Ra ratio. There was no significant increase in IL-β levels. IL-1Ra levels were increased at 12 h, but the IL-1β/IL-1Ra ratio had decreased at 3 h after the epileptic seizure. We think that this result reflects the fast and small increase of IL-1β that did not reach statistical significance. In this respect, the IL-1β/IL-1Ra ratio may provide more important information than the IL-1Ra and IL-1β levels separately.

Experimental status epilepticus in rodents induced IL-6 levels in the hippocampus.[37,38] When exogenously applied, IL-6 increased the severity of chemically induced seizures in rats.[30] In clinical studies, a rapid and transient post-ictal increase of IL-6 increase, which peaked at 12 h and remained for 24 h, has been demonstrated.[11,12,22,16] Our study results confirm these clinical trials with significantly increased IL-6 levels at 12 h. The origin of the increased cytokine levels in peripheral blood is discussed in the literature. The rapidity of the changes in cytokine levels, the correlation of the increase in cytokines with seizure severity and more significant changes in the CSF than in the plasma supports intra-thecal synthesis.[13,23] Lehtimäki et al. suggested that increased serum levels of cytokines originate mainly from the endothelial cells of the brain vessels and partially from the CSF compartment via venous drainage.[23] The up-regulation of IL-6 is found to be correlated with the severity of the seizure.[13,23] Alapirtti et al. suggested that seizure-induced IL-6 production is more significant in patients with TLE than in patients with XLE. They attributed this result to the effects of TLE on the hypothalamus-pituitary axis resulting in different immunological responses.[22] Different patterns of cytokine release may also exist between different types of TLE; higher levels of IL-6 in patients with right-sided seizure origin and lower levels of IL-6 in patients with hippocampal sclerosis supports the neuroprotective role of IL-6 that was observed by Bauer et al.[16]

Induced IL-1Ra and IL-6 levels at 12 h were more significant among patients with high baseline IL-1β and low baseline IL-1Ra concentrations. Baseline IL-1Ra levels were greater than 200 pg/ml in only two of our patients (Table 2). Therefore, the relationship between low baseline IL-1Ra concentrations and increased cytokine levels at 12 h may be inconclusive, but we think that the association of the high baseline IL-1β levels and the inducibility at 12 h is remarkable.

Our study confirms previous results showing post-ictal changes in IL-1β, IL-1Ra and IL-6 levels.[11–13,22] We documented cytokine levels in the immediate post-ictal period and in the following 24 h, so our results are not confounded by the short half-lives of the cytokines. The timeline of the post-ictal increase on IL-6 and IL-1Ra levels in our study were similar to previous reports[22,16] (Figs. 1 and 2). Neuronal damage may induce cytokine release, and

Table 6
IL1β/IL-1Ra concentrations.

	Baseline	0 h	3 h	6 h	12 h	24 h
TLE	20.42 ± 15.09 (0.26–42.59)	18.42 ± 14.28 (0.21–34.25)	16.59 ± 14.47 (3.21–33.38)	13.11 ± 15.08 (0.46–31.85)	10.93 ± 15.09 (0.2–39.93)	9.18 ± 6.15 (1.92–19.59)
XLE	29.74 ± 22.09 (0.68–60.91)	27.04 ± 18.43 (6.81–61.56)	22.76 ± 20.53 (0.81–60.79)	27.54 ± 22.37 (1.05–59.02)	29.41 ± 21.91 (0.93–61.47)	33.12 ± 27.15 (4.09–84.31)
IGE	17.04 ± 18.12 (0.45–58.42)	18.47 ± 13.1 (1.26–34.39)	10.05 ± 11.16** (0.79–28.7)	25.54 ± 41.08 (0.31–131.72)	15.26 ± 14.97 (0.31–38.9)	82.35 ± 179.15 (0.29–557.16)
Total	22.34 ± 18.94 (0.26–60.91)	21.43 ± 15.31 (0.21–61.56)	16.18 ± 16.07* (0.79–60.79)	22.99 ± 29.35 (0.31–131.72)	19.05 ± 18.68 (0.2–61.47)	46.14 ± 113.51 (0.29–557.16)

Baseline: before the seizure; 0 h: Immediate post-ictal state. Values in mean ± SD.
* 3 h > baseline ($p = 0.03$).
** 3 h > baseline ($p = 0.01$).

seizure-related neuronal damage must be considered when assessing post-ictal increases in interleukin levels. By excluding cases of acute symptomatic seizures, we assume to have mostly eliminated this factor. We aimed to evaluate the influence of the different epilepsy syndromes on the post-ictal cytokine profiles. A limitation of the study was the small number of cases. Furthermore, depth recordings were not available in our study, but we carefully classified epilepsy types with clinical, radiological and video-EEG findings. Nevertheless, we could not observe a more significant IL-6 increase in the TLE group as mentioned in some of the recent studies.[22]

5. Conclusion

Both experimental and human data suggest a link between the cytokine network and epileptic seizures. However, the mechanism and clinical implications of these epilepsy-related immune alterations need to be clarified with a goal of developing potential anti-epileptic treatment strategies.

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