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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)