Interleukin 18 (IL-18) and its binding protein (IL-18BP) are increased in patients with epilepsy suggesting low-grade systemic inflammation

Monika Mochol[a,b,c,*], Erik Taubøll[b,c], Pål Aukrust[c,d], Thor Ueland[c,e,f], Ole A. Andreassen[g], Sigrid Svalheim[b]

[a] Department of Neurology, Østfold Hospital Trust, Norway
[b] ERGO – Epilepsy Research Group of Oslo, Department of Neurology, Oslo University Hospital, Norway
[c] Institute of Clinical Medicine, University of Oslo, Norway
[d] Department of Immunology and Infectious Disease, Oslo University Hospital, Norway
[e] Research Institute of Internal Medicine, Oslo University Hospital, Norway
[f] K.G. Jebsen Thrombosis Research and Expertise Center, University of Tromsø, Norway
[g] NORMENT Centre, Institute of Clinical Medicine, University of Oslo and Division of Mental Health and Addiction, Oslo University Hospital, Norway

ARTICLE INFO

Keywords:
Antiseizure medication
Epilepsy
Epileptogenesis
Interleukin-18
Interleukin-18 binding protein
Neuroinflammation

ABSTRACT

Purpose: Proinflammatory cytokines seems to play a role in epileptogenesis independent of the underlying cause. The purpose of this study was to assess if IL-18 and its binding protein IL-18BP are related to epilepsy and could act as a predictive biomarker for epileptogenesis.
Methods: In this cross-sectional study, circulating levels of IL-18 and IL-18BP were analysed in 119 epilepsy patients, and 80 healthy controls. Participants completed a questionnaire regarding epilepsy, use of drug(-s) and comorbidity.
Results: Epilepsy patients had significantly higher serum levels of IL-18 ($p = 0.003$) and IL-18BP ($p = 0.009$) than healthy controls. The groups differed in sex, age and weight, however none of those variables were significantly correlated with IL-18 and IL-18BP in patients or controls. Weight was considered an important confounder in our study. Subgroup investigations revealed that in participants with BMI under 30 kg/m², serum IL-18 ($p = 0.032$) and IL-18BP ($p = 0.029$) remained significantly higher in patients than controls. Further analyses showed significantly higher concentration of IL-18 among participants using carbamazepine (CBZ) ($p = 0.016$) or lamotrigine (LTG) ($p = 0.024$), but not in those using levetiracetam (LEV) ($p = 0.102$) compared to controls. No associations were found between serum levels of IL-18 and IL-18BP and epilepsy duration, seizures type, or presence of seizures in the last six months.
Conclusion: The study shows an elevation of IL-18 and IL-18BP serum levels in epilepsy patients. This result indicates the presence of a low-grade systemic inflammation involving IL-18 in epilepsy. Further investigations should explore the character and clinical impact of IL-18 as well its possible role as a biomarker for epilepsy.

1. Introduction

Current epilepsy treatment is mostly symptomatic and seems not to influence the underlying pathology or progression of the disease [1,2]. One-third of the patients are resistant to current therapies and possible mechanisms responsible for drug resistance are still unknown [2–4]. Polytherapy with antiseizure medications (ASM) is often required in those patients. The lack of evidence-based guidelines for drug-resistant epilepsy remains a clinical challenge [5].

The presence of inflammation, without known autoimmune or infectious etiology has been reported in epilepsy in the past two decades, and has been considered an important mechanism for epileptogenesis [for review see [4,6–8]]. A 'neuromodulatory' role of various inflammatory molecules like cytokines, chemokines and prostaglandins in epilepsy models has been described by both a direct action on neurons, and by an autocrine receptor stimulation in glia cells which influence glianeuronal communication [3,9,10].

Interleukin (IL)-18, a classical inflammatory cytokine related to the IL-1 family are among others released from NLRP3 inflammasomes. IL-18 may be synthesized in central nervous system (CNS), and its receptors are expressed in neurons [11–13]. Studies in rodent brain revealed the presence of IL-18 transcript in various regions like

* Corresponding author at: Department of Neurology, Østfold Hospital Trust, Postboks 300, 1714 Grålum, Norway.
E-mail address: monikamochol@hotmail.com (M. Mochol).

hippocampus, amygdala, hypothalamus, cerebral cortex and cerebellum [14–17], and microglia and astrocytes seem to produce IL-18 [18,19]. In humans, several studies revealed higher IL-18 levels in serum and cerebrospinal fluid in patients with multiple sclerosis (MS) [11,20–22]. In Alzheimer's disease and vascular dementia higher levels correlated with cognitive decline [23–26]. The biological effects of IL-18 are augmented by the IL-18 binding protein (IL-18BP) that binds to IL-18 with an affinity significantly higher than that of IL-18 receptor α chain (IL-18Rα) [27,28]. So far, data on the regulation of IL-18BP in brain diseases are scarce.

The role of IL-18 in relation to epilepsy and seizures is not clarified. The level of IL-18 has been shown to be increased after kainic acid (KA) induced excitotoxic and hypoxic-ischemic brain injury. This finding suggests that IL-18 has a role in neurodegeneration and contributes to cellular damage [11,29–31]. In contrast, some papers have reported a protective effect of IL-18 in rats with status epilepticus (SE) [32,33]. Moreover, Jung et al. concluded that IL-18-related mechanisms maintain permeability of the blood-brain barrier (BBB) by an up-regulation of dystrophin expression, which leads to a reduction of vasogenic oedema. However, so far human data on IL-18 in relation to epilepsy and seizures, are lacking.

We hypothesized that IL-18 could be involved in the development and progression of epilepsy and in the present study we examined serum levels of IL-18 and IL-18BP in epilepsy patients and healthy controls. We also investigated if IL-18/IL-18BP was related to clinical characteristics like seizure frequency, seizure types or epilepsy duration.

2. Methods

2.1. Participants

119 patients with epilepsy and 80 healthy controls participated in the current cross-sectional study. All epilepsy and seizure types were included in the study and classified according to the International League Against Epilepsy classifications [34–36]. The patients were recruited from the outpatient clinics at Oslo University Hospital and Østfold Hospital, Norway. Inclusion criteria for all participants were age above 18 years, lack of autoimmune disorders, not mentally retarded and no drug or alcohol abuse. Patients should have been treated with carbamazepine (CBZ), lamotrigine (LTG) or levetiracetam (LEV) in monotherapy for at least six months. Exclusion criteria were use of any other ASM for the last year before inclusion, the use of anti-inflammatory medications and oral contraceptives in women. The control group was recruited among students, hospital staff and the general population of Oslo. All participants completed standardised questionnaires on demographic and clinical characteristics, with particular focus on comorbidity. Based on this clinical evaluation all controls were considered as apparently healthy.

The study was approved by The Regional Committee for Medical and Health Research Ethics (REC Norway), and has been performed in accordance to the ethical standard in the Declaration of Helsinki. All participants received both oral and written information about the study and signed informed consent was mandatory.

2.2. Data collection

Epilepsy duration was defined as the period from the first epileptic seizure to inclusion. Patients were divided into three groups according to the use of ASM with either CBZ, LTG or LEV. Subgroups were created on the basis of: (i) most frequent types of seizures (generalized versus focal), (ii) number of seizures during lifetime, and (iii) presence of seizures in the last six months before inclusion. Participants with less than five epileptic seizures in total were classified as 'low seizure frequency during the lifetime', patients with between five and ten attacks were ranked as 'moderate seizure frequency', and those with more than ten seizures during lifetime were classified as 'high seizure frequency'.

Height and weight data was collected and body mass index (BMI) was calculated as weight in kilograms divided into height in square meters (kg/m²). For subgroup analysis we identified obese subjects with BMI over 30 kg/m².

2.3. Cytokine measurements

Venous blood samples were obtained in the morning. Plasma was isolated immediately after blood collection and stored at -80° C. IL-18 (Cat# DY318-05) and IL-18BP (Cat# DY119) levels were analyzed using antibodies from RnDsystems (Stillwater, MN) in duplicate in a 384-well format using a combination of a SELMA (Jena, Germany) pipetting robot and a BioTek (Winooski, VT, USA) dispenser/washer. Absorption was read at 450 nm with wavelength correction set to 540 nm using an ELISA plate reader (BioTek). Intra- and inter-assay coefficients were < 10 % for both. No significant diurnal variation was observed in IL-18 and IL-18BP levels in samples isolated at 0800 and 1200 ($n = 6$) and no difference in fasting vs. non-fasting levels ($n = 6$). IL-18 and IL-18BP were stable, 101 % and 99 % of IL-18 and IL-18BP, respectively, was present in samples that were stored at RT for 24 h. Sensitivity, defined mean of the blank + 3 SD, was 22 and 25 pg/mL for IL-18 and IL-18BP, respectively.

2.4. Statistical analyses

Demographic data, clinical characteristics and subgroup analysis are presented by use of descriptive statistics, including frequency and proportions for categorical variables, and mean with standard deviation (SD) or median with range and quartile deviation (QD) for continuous variables. Comparison between groups was done by Pearson's chi-squared test, student's *t*-test and Mann-Whitney U test, as appropriate. Coefficient of correlation was calculated by Spearman rank test. Analyses including correction for potential confounders was done by linear regression on log transformed values of IL-18, IL-18 BP and age. Probability values (two-sided) were considered significant at $p < 0.05$. All calculations were performed with SPSS for Windows statistical software (Version 25.0; SPSS Inc, Chicago, IL).

3. Results

3.1. Characterization of the study group

One hundred and twenty-one patients with epilepsy were included in the study. Two of them were excluded due to presence of autoimmune disease rendering a total of 119 patents. For comparison we also included 80 healthy controls. Demographic parameters are given in Table 1. The epilepsy patients had a higher percentage of men ($p = 0.003$), were slightly older ($p = 0.004$), and had a higher BMI ($p < 0.001$) than healthy controls (Table 1).

Mean age at seizure onset was 20.5 years and mean disease duration was 10 years. We assembled information about total numbers of seizures from 112 subjects. Fifty-seven patients (50.9 %) had 'low seizure frequency', 19 (17 %) with 'moderate seizure frequency' and 36 (32.1 %) subjects 'high seizure frequency' (see data collection section for definitions). We were able to collect details about type of epilepsy- and seizures from 113 participants. Focal epilepsy was identified in 78 (69 %) patients whereas 35 (31 %) had generalized epilepsy. Forty (35.4 %) had focal seizures with or without impaired awareness, 70 (61.9 %) had generalized tonic-clonic seizures including both primary generalized and focal to bilateral tonic-clonic seizures.

Patients used three different ASMs in monotherapy at the time of study enrolment, which allowed to create subgroups. Fifty-five persons (46 %) used CBZ, 49 (41 %) used LTG and 15 (12 %) were treated with LEV.

Table 1
Demographic characteristics of all study participants.

	Controls	Patients	P-value	CBZ	LTG	LEV
Gender n (%)	80	119	p = 0.003			
Male	36 (45.0)	79 (66.4)		40 (72.7)	29 (30.4)	10 (66.7)
Female	44 (55.0)	40 (33.6)		15 (27.3)	20 (31.9)	5 (33.3)
Age (years) mean (SD)	29.2 (±8.0)	32.3 (±7.4)	p = 0.004	33.7 (±6.6)	31.0 (±7.8)	31.3 (±8.3)
Male	28.1 (±7.9)	32.1 (±7.8)		33.4(±7.0)	30.4 (±8.2)	31.7 (±9.3)
Female	30.0 (±8.1)	32.7 (±6.7)		34.4 (±5.6)	31.9 (±7.3)	30.6 (±6.9)
BMI (kg/m²) mean (SD)	22.9 (±2.7)	25.6 (±4.3)	p < 0.001	25.6 (±4.4)	25.7(±4.2)	25.1 (±4.5)
BMI < 30 (kg/m²) mean (SD)	22.9 (±2.7)	24.3 (±3.1)	p = 0.003	24.4 (±3.3)	24.5(±2.9)	23.1 (±3.1)
Age at seizure onset (years) mean (SD)		20.5 (±9.6)		17.8 (±9.2)	22 (±8.9)	25.5 (±10.5)
Epilepsy duration (years) mean (SD)		11.9 (±9.0)		15.9 (±9.1)	9.2 (±8.0)	5.9 (±4.7)
Etiology n (%)						
unknown		62 (62.0)		29 (63.0)	28 (66.7)	5 (41.7)
Post-traumatic		11 (11.0)		2 (4.3)	6 (14.3)	3 (25.0)
tumor		6 (6.0)		2 (4.3)	3 (7.1)	1 (8.3)
AVM		4 (4.0)		3 (6.5)	1 (2.4)	n.a
meningitis/encephalitis		3 (3.0)		1 (2.2)	1 (2.4)	1 (8.3)
abscess		1 (1.0)		1 (2.2)	n.a	n.a
MTLE		2 (2.0)		1 (2.2)	1 (2.4)	n.a
stroke		2 (2.0)		1 (2.2)	n.a	1 (8.3)
others		9 (9.0)		6 (13.2)	2 (4.8)	1 (8.3)
Types of epilepsy						
Focal		78 (69.0)		37 (64.9)	30 (65.2)	11 (78.6)
Generalized		35 (31.0)		16 (30.2)	16 (34.8)	3 (21.4)
Types of seizures n (%)						
FA/FIA		40 (35.4)		19 (35.9)	16 (34.7)	5 (35.7)
FBTC/GTC		70 (61.9)		34 (64.2)	27 (58.7)	9 (64.3)
GAS		3 (2.7)		n.a	3 (6.5)	n.a

n: number; SD: standard deviation; BMI: body mass index; FA: focal with intact awareness; FIA: focal with impaired awareness; GTC: generalized tonic-clonic; FBTC: focal to bilateral tonic-clonic; GAS: generalized absence seizures; n.a: not applicable.

Table 2
Level of inflammatory markers in controls and patient and sort by BMI.

	IL-18 (pg/mL)			p-value vs controls	IL-18BP (ng/mL)			p-value vs contols	Ratio IL-18/IL-18BP			p-value vs controls
	Median	QD	Range		Median	QD	Range		Median	QD	Range	
Controls	232.9	63.6	[125.0–520.8]		4.8	1.0	[0.8–11.7]		47.3	12.5	[24.8–156.7]	
All patients	273.4	86.7	[125.0–751.4]	0.003	5.4	1.3	[0.2–23.1]	0.009	53.3	10.8	[11.6–625.0]	0.113
CBZ n=55	309.4	95.1	[125.0–707.6]	0.016	5.4	1.5	[0.2–14.8]	0.161	58.1	9.6	[31.2–625.0]	<0.01
LTG n=49	257.6	81.3	[125.0–751.4]	0.024	5.4	1.1	[2.4–9.0]	0.037	52.1	11.0	[29.2–91.9]	0.369
LEV n=15	284.6	95.1	[156.4–527.6]	0.102	5.7	1.1	[4.5–23.1]	0.003	40.4	15.3	[11.6–90.8]	0.202
BMI < 30												
All patients	264.4	85.0	[125.0–751.4]	0.032	5.4	1.2	[0.8–23.1]	0.029	52.1	11.0	[11.6–164.2]	0.287
CBZ n=45	282.1	87.2	[125.0–516.4]	0.08	5.2	1.5	[0.8–10.2]	0.304	57.6	9.8	[31.2–164.2]	0.054
LTG n=41	283.7	85.2	[125.0–751.4]	0.082	5.5	1.1	[2.4–9.0]	0.04	52.4	11.2	[29.2–91.9]	0.665
LEV n=11	272.6	91.7	[156.4–444.4]	0.381	7.2	0.6	4.5–23.1]	0.045	47.2	18.8	[11.6–90.8]	0.263
BMI > 30												
All patients	361.1	121.5	[125.0–707.6]	<0.001	6.5	1.8	[0.2–14.8]	0.07	59.2	10.1	[28.7–625.0]	0.04
CBZ n=8	379.7	204.2	[125.0–707.6]	0.012	6.0	2.2	[0.2–14.8]	0.207	65.6	14.0	[47.1–625.0]	0.005
LTG n=7	327.4	89.5	[221.6–478.1]	0.033	5.8	1.6	[3.8–8.9]	0.175	53.5	5.8	43.6–75.6]	0.261
LEV n=4	354.4	129.1	[210.4–527.6]	0.065	7.2	2.2	[6.5–12.1]	0.004	44.0	12.2	28.7–61.0]	0.509

IL-18: interleukin18; IL-18BP: Interleukin 18 binding protein; BMI: body mass index; n: number; QD: QD: quartile deviation; CBZ: carbamazepine; LTG: lamotrigine; LEV: levetiracetam.

Table 3
Bivariate correlations with Spearman coefficients and p-value between inflammatory markers and clinical characteristics of epilepsy patients.

		IL-18	IL-18BP	ratio IL-18/IL-18BP
Epilepsy duration	Correlation Coefficient	0.071	−0.04	0.181
	p- value	0.447	0.626	0.051
Seizure type (generalised vs. focal)	Correlation Coefficient	−0.073	−0.067	0.028
	p-value	0.439	0.479	0.769
Presence of seizures in last 6 months	Correlation Coefficient	−0.125	−0.175	−0.012
	p-value	0.174	0.056	0.894
Seizures frequency low	Correlation Coefficient	−0.016	−0.021	0.035
	p-value	0.865	0.824	0.718
moderate	Correlation Coefficient	0.060	−0.028	0.040
	p-value	0.530	0.767	0.675
high	Correlation Coefficient	−0.031	0.046	−0.069
	p-value	0.748	0.634	0.469

Correlation is significant at the $p < 0.05$. IL-18: interleukin18; IL-18BP: interleukin 18 bindings protein.

3.2. *Serum levels of IL-18 and IL-18BP*

Epilepsy patients had significantly higher ($p = 0.003$) serum level of IL-18 (median: 273.4 pg/mL) compared to healthy controls (median: 232.9 pg/mL) (Table 2). Subgroup analyses showed significantly higher concentration of IL-18 among participants using CBZ ($p = 0.016$) or LTG ($p = 0.024$), but not in those using LEV ($p = 0.102$) compared to controls (Table 2).

Serum concentration of IL-18BP was also significantly higher ($p = 0.009$) in epilepsy patients than control subjects (Table 2). Level of IL-18BP was significantly increased in patients using LTG ($p = 0.037$) and LEV ($p = 0.003$), but not in those using CBZ ($p = 0.161$).

Ratio IL-18/IL-18BP was significantly higher only in CBZ treated patients (Table 2).

The patient and control group differed in sex, age and weight, however none of those variables were significantly associated with levels of IL-18 or IL-18BP.

Weight was considered an important confounder in our study, as adipose tissue might be a source of circulating IL-18. Subgroup investigations revealed that in participants with BMI under 30 kg/m², serum IL-18 ($p = 0.032$) and IL-18BP ($p = 0.029$) remained significantly higher in patients than controls (Table 2).

No association was found between serum level of IL-18 and IL-18BP related to epilepsy duration, epilepsy- or seizures types, numbers of seizures, or presence of seizures in the last six months (Table 3).

4. Discussion

The main finding in the current study is higher level of IL-18 in epilepsy patients. Whereas there was significant increase in two medication subgroups, we could not find any significant associations to clinical characteristics of the epilepsy patients. Our findings may further support a role of inflammation in the pathogenesis of epilepsy with IL-18 as a potential mediator.

IL-18 has previously been reported to be elevated in various autoimmune, infectious and cardiovascular diseases. There are also some reports of raised serum levels of IL-18 in brain disorders like MS and Alzheimer's disease [21–26,37]. In the present study we show that epilepsy patients were also characterized by increased levels of IL-18BP. Our findings show regulation of the IL-18/IL-18BP dyad in patients with epilepsy, the potential pathogenic consequences of this finding are still unclear.

We did not identify any correlation between IL-18 and IL-18BP and epilepsy duration, seizure- or epilepsy types, total numbers of seizures or presence of seizures in the last six months. This suggests that the higher level of these markers is related to epilepsy *per se*. However, patients included in our study had predominantly a stable and well controlled epilepsy. We cannot rule out that the levels of markers could be higher in patients with more refractory epilepsy or in the acute phase immediately after seizures or SE.

In contrast to the lack of association with seizure characteristics, we found a significant association with medications. Thus, the ratio IL-18/IL-18BP was significantly increased in those treated with CBZ. It was unchanged in LTG treated patients, and decreased after LEV treatment. As this ratio may give an indication of inflammatory activity in the IL-18 system, it is tempting to speculate whether this could be of any clinical relevance for epileptogenesis in which inflammation is crucial [8]. LEV has been considered as a drug with probable antiepileptogenic properties [41,42], while no such effects have been observed for the other two drugs [39,40]. However, the complex interplay between epileptogenesis, inflammation and ASM is mainly unknown.

Our study groups differed in age, sex and weight. Studies on obese individuals with BMI over 30 kg/m² and high percent of visceral adipose tissue, have shown increased production of IL-18 in comparison to lean controls. This can suggest that adipose tissue might be a source of circulating IL-18 in this population [38,39]. However, not all studies indicate association between fat tissue with increased level of IL-18. Hung et al. concluded that elevated serum level of IL-18 is a risk predictor for metabolic syndrome, independent of obesity and insulin resistance [40]. In the present study BMI was not significantly correlated with IL-18 or IL-18BP levels in patients or controls. Moreover, the level of IL-18 and its binding protein remained significantly higher in epilepsy patient group with BMI under 30 kg/m². This indicates that low-grade systemic inflammation involving IL-18 mediated mechanisms is present in those patients.

Mean age difference between groups was 3.1 years which brings the question if this variance is biologically important. It is expected that comorbidity increases with aging. We did not find consequential comorbidity within study groups.

The activity of IL-18 can be regulated by IL-37. This cytokine binds to IL-18Rα although with lower affinity than IL-18 [41–44]. IL-37 interacts with IL-18BP and reduces the ability of interferon (INF)-γ production from natural killer (NK) cells induced by IL-18. This neutralizing effect was observed only at a low concentration of IL-18BP [44]. IL-37 interacts with IL-18BP and reduces the ability of INF-γ production from natural killer (NK) cells induced by IL-18. This neutralizing effect was observed only at a low concentration of IL-18BP [28,44]. High levels of IL-37 may be protective in some inflammatory diseases, but low levels may contribute to increased disease severity [43,45]. Coll-Miro et al. reported that IL-37 transgenic mice suffering from traumatic spinal cord injuries exhibited greater mobility compared to wild type mice subjected to the same injury [43,46]. However, IL-37 is not expressed in tissue from healthy subjects and the role of endogenous IL-37 in human CNS remains unknown [45,46].

Based on experimental studies in animal models, IL-18 has been suggested to promote neurodegeneration in a dose-dependent manner and to contribute to hypoxic ischemic brain damage [30]. On the other hand, IL-18 may also have protective effects in epilepsy by inducing INF-γ mediated neuroprotection with enhanced recovery of the intracellular Ca^{2+} level, following exposure to glutamate during epileptic seizures [33]. IL-18 has also been suggested to enhance BBB permeability after seizure-induced brain injury [17], playing a potential role in epileptogenesis. Moreover, Alzheimer-prone mice with IL-18

deficiency have shown an increased seizure frequency. Tzeng et al. found that acute injection of IL-18 reduced excitatory synaptic transmission in hippocampus [37]. Thus, based on experimental data so far, IL-18 could have both protective and harmful effects in epileptogenesis, and its role in epilepsy patients is still unclear.

Several study limitations are acknowledged. Because of the cross-sectional study design, a direct association between IL-18 and IL-18BP concentration and the epilepsy cannot be established. In the present study we measured total concentration of IL-18, ideally free IL-18 should have been measured. Another limitation is the lack of data on fasting levels of cholesterol and glucose, which could help identify individuals with undiagnosed/untreated diabetes, hypercholesterolemia or metabolic syndrome, factors of importance for IL-18. Furthermore, serum levels may not necessarily reflect IL-18 levels within CNS. A higher number of subjects would also be valuable, especially for subgroup analyses to avoid type II errors.

5. Conclusion

In conclusion, our study is the first to show increased serum levels of IL-18 and its binding protein,

IL-18BP in epilepsy patients. Further studies should examine if IL-18 is a mediator in the progression of epilepsy, and thereby also a potential target for therapy, as well as describing the relevant disease mechanisms.

Declaration of Competing Interest

Ole A. Andreassen has received consultant honorarium form HealthyLytix. None other authors have any conflict of interest to declare.

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