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Blood levels of cytokines in children with idiopathic partial and generalized epilepsy

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ABSTRACT

Purpose: Antiepileptic drugs have been reported to reduce the levels of serum immunoglobulins and affect the production and levels of certain cytokines. We investigated the effects of valproic acid (VPA) and topiramate (TPM) on the blood levels of interleukin (IL)-1α, IL-1β, IL-6, IL-10, and TNF-α in children with idiopathic generalized and partial epilepsy.
Methods: Forty prepubertal children aged 6–12 (mean 8.3 ± 1.7) years, 19/40 (47.5%) female and 21/40 (52.5%) male, with idiopathic generalized or partial epilepsy diagnosed in the child neurology outpatient clinic were included. The patients were divided into two treatment groups: 20 were treated with VPA and 20 with TPM. The plasma levels of IL-1α, IL-1β, IL-6, IL-10, TNF-α were measured using ELISA method before the initiation of treatment and at the 6th and 12th months of the treatment. The Chi-square test was used to compare qualitative data. To compare the periods, recurrence measurements were done using variance analysis and Freidman 2-sided variance analysis. $p < 0.05$ was considered as statistically significant.
Results: In the VPA group, the levels of IL-1α significantly increased at 12 months while the levels of IL-10 decreased at 6 months of treatment compared to values before treatment ($p < 0.05$). There was no significant difference in levels of IL-1β, IL-6, TNF-α ($p > 0.05$). In the TPM group, lower levels of IL-10 were observed at 6th and 12th months compared to the onset of treatment ($p < 0.05$).
Conclusion: The results of this study demonstrated that VPA and TPM might lead to changes in the levels of cytokines in epileptic patients. The next step would be to investigate the relation of these findings to the outcome of epilepsy and response to treatment.

1. Introduction

Epilepsy is a disease affecting 0.5–1% of the child population.[1] Efficient anti-epileptic treatment is available for most cases, although hematological, biochemical and gastrointestinal side effects are not rare in long-term use. Anti-epileptic drugs also act on the immune system.[2] They reduce the serum levels of immunoglobulins[3–5] and affect the production of cytokines.[1]

Cytokines are chemical conduction molecules which mediate the development and regulation of the inflammatory and immune responses.[1–5] The bidirectional correlation between the central nervous system (CNS) and immune system is mostly mediated by cytokines.[6,7] Inflammation may facilitate if not cause the development of epilepsy, epileptic seizures can trigger an inflammatory response.[8] Experimental and clinical findings support a crucial role of inflammatory processes in epilepsy.[9] Interleukin-1 receptor antagonist (IL-1Ra) has neuroprotective effects in experimental status epilepticus[10], and IL-6 has neuroprotective and anticonvulsive effects after kainic acid-induced status epilepticus.[11] Increased levels of IL-6 and IL-1Ra were reported after single generalized or prolonged seizures.[12] Increased post-ictal serum levels of IL-6, IL-1β, IL-2, IL-4 and interferon (IFN)-γ were described by Sinha et al.[13]

Recent studies reported that certain anti-epileptic drugs (AEDs) have important effects on the production of inflammatory cytokines.[5,14,15] The action of AEDs might even affect their impact

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Table 1
The distribution of the patients in Group I and Group II by gender and type of seizure.

Type of seizure	Group 1 ($n=20$)		Group 2 ($n=20$)		Total ($n=40$)
	Female	Male	Female	Male	
	($n=10$, %50)	($n=10$, %50)	($n=9$, %45)	($n=11$, %55)	($n=40$, %100)
Generalized	3 (%30)	2 (%20)	1 (%11, 11)	0 (%0)	$n=6$ (%15)
Partial	7 (%70)	8 (%80)	8 (%88, 89)	11 (%100)	$n=34$ (%85)

on epileptic seizures.[16] However, the underlying mechanisms have not been fully understood. In particular, reports on the effect of AEDs on interleukin (IL) levels have been scarce and conflicting.[2,14,15,17] We therefore aimed to investigate the effects of valproic acid (VPA), an old-generation AED, and topiramate (TPM), a newer AED on the blood levels of IL-1α, IL-1β, IL-6, IL-10 and tumor necrosis factor (TNF)-α.

2. Methods

We enrolled a total of 40 prepubertal patients, 19 (47.5%) females and 21 (52.5%) males, whose ages ranged between 6 and 12 years (mean 8.3 ± 1.7 years). These patients presented with seizures to the outpatient clinic of pediatric neurology between 2009 and 2010 and were diagnosed with idiopathic generalized or partial epilepsy, based on history, neurologic examination, electroencephalography (EEG), and magnetic resonance imaging (MRI).

Exclusion criteria included mental retardation, abnormal findings on neurologic examination or MRI, previous history of status epilepticus, previous history of AED use, immunosuppressive therapy, autoimmune disease, thyroid, liver or kidney disease, immune deficiency, or the presence of an infection at the time of diagnosis.

The patients were treated with VPA or TPM according to clinical or EEG findings: as both drugs are effective in generalized and partial seizures, the treatment decision was made considering the child's age, sex, and body weight. Group I consisted of 20 patients treated with VPA 20 mg/kg/day and Group II of 20 patients treated with TPM 3 mg/kg/day. TPM was initiated at the dose of 0.5 mg/kg/day, and was increased by 1 mg/kg/day once a week up to 3 mg/kg/day.

Ethical approval was obtained from the Ethical Board of Karadeniz Technical University, Faculty of Medicine (date: 23.03.2009, number: 2009/28).

All measurements were made in venous blood samples obtained between 7:30 and 8:30 a.m. following a fasting period of at least 10–12 h initially and at least 10–12 h after the last AED intake at the 6th and 12th months. Three samples were drawn from each patient: at baseline, and at the 6th and 12th months of treatment. Care was taken to obtain the samples during an infection-free and seizure-free period of at least one week. Samples were centrifuged at 3000 rpm for 15 min and sera were stored at −80 °C until the study. On the study day, all sera were thawed at the same time and tested on the same day for IL-1α, IL-1β, IL-6, IL-10, and TNF-α (Assay-Pro, USA) levels using the enzyme-linked immunosorbent assay (ELISA) method. Baseline, and 6th and 12th month measurements were compared.

The AED levels were not measured at the various time points when blood sampling was performed (6th and 12th months).

2.1. Statistical analysis

Statistical analyses were performed using The Statistical Package for The Social Sciences software (SPSS 13.0.1 serial number: 9069728). Descriptive statistics were used.

The Chi-square test was used to compare qualitative data. In each group, conformity of the measured values to the normal distribution was analyzed by using Kolmogorov–Smirnov test. Variation during the period for the data showing skewed distribution was analyzed using Friedman test and $p < 0.005$ was determined as statistically significant. *Post hoc* by Wilcoxon test using Bonferroni correction to adjust for multiple comparisons in each group.

3. Results

Thirty-four subjects (85%) were diagnosed with idiopathic partial epilepsy and 6 (15%) with idiopathic generalized epilepsy. Group I included 20 patients, 10 males (50%) and 10 females (50%), and Group II 20 patients, 9 (45%) females and 11 (55%) males (Table 1). There was no significant difference in the age and gender distribution of the two treatment groups. The most common seizure types were complex partial (55%) and simple partial (30%) (Table 2). The most common EEG finding was focal epileptiform activity (75%) (Table 2). The rate of seizure control was similar between the two groups.

3.1. Laboratory findings

In Group I, treated with VPA, the levels of IL-1α were increased at the 6th and 12th months, with the 12-month level being significantly increased compared to baseline ($p < 0.05$) (Table 3). No significant change was observed in the levels of IL-1β, IL-6, and TNF-α ($p > 0.05$) (Table 3).

The levels of IL-10 showed a significant decrease compared to baseline at 6th month of VPA treatment ($p < 0.05$) (Table 3).

In Group II treated with TPM, the levels of IL-10 diminished significantly at the 6th and 12th months compared to pre-treatment levels (Table 4). Alterations in the levels of other cytokines were not significant (Table 4).

4. Discussion

Studies in epileptic patients and also in animal models revealed changes in the expression of cytokines and immune cells.[12,18,19] Moreover, the anticonvulsive activity of anti-inflammatory drugs, namely steroids and ACTH, even on seizures which that are refractory to other AEDs, suggest that inflammation may play a role in the pathogenesis of the epilepsy.[9,20,21]

Table 2
Types of seizures and EEG results of the patients.

Type of seizure	*n*	%	EEG findings	*n*	%
Simple partial	12	30	Epileptiform activity		
Complex partial	22	55	Focal	30	75
JTK	3	7.5	Generalized	8	20
Tonic	1	2.5			
Clonic	1	2.5	Paroxysmal anomaly	2	5
Absence	1	2.5			
Total	40	100	Total	40	100

Table 3
Levels of IL-α, IL-1β, IL-6, IL-10, TNF-α at baseline, 6th month and at 12th month of treatment with valproic acid.

Cytokines	Baseline	6th month	12th month	p^*
IL-1α (pg/mL)	195.50 ± 105.65[a]	208.50 ± 117.66	231.50 ± 110.41[b]	0.017
IL-1β (pg/mL)	18,222.74 ± 29,265.65	11,075.00 ± 19,041.65	11,289.13 ± 18,773.35	0.705
IL-6 (ng/mL)	18.23 ± 19.85	13.26 ± 15.86	13.65 ± 14.33	0.086
IL-10 (ng/mL)	2562.55 ± 4065.35[d]	1470.32 ± 2599.27[e]	1609.07 ± 2646.96	0.006
TNF-α (ng/mL)	44.56 ± 50.72	34.58 ± 8.01	44.66 ± 39.10	0.861

a–b and d–e: Significant difference at the level of $p < 0.05$.
* Freidman test.

Table 4
Levels of IL-α, IL-1β, IL-6, IL-10, TNF-α at baseline, at 6th month and at 12th month of the treatment with topiramate.

Cytokines	Baseline	6th month	12th month	p^*
IL-1α (pg/mL)	180.00 ± 47.46	63.00 ± 52.92	183.50 ± 82.09	0.163
IL-1β (pg/mL)	3822.54 ± 5489.41	4364.95 ± 5494.85	3119.46 ± 3672.47	0.705
IL-6 (ng/mL)	10.81 ± 24.31	9.73 ± 17.45	8.58 ± 13.13	0.705
IL-10 (ng/mL)	474.82 ± 544.44[a]	415.50 ± 647.63[b]	310.97 ± 366.36[c]	0.003
TNF-α (ng/mL)	40.83 ± 47.46	38.92 ± 36.25	35.48 ± 20.09	0.951

a–b: Significant difference at the level of $p < 0.05$ Wilcoxon test using Bonferroni correction.
a–c: Significant difference at the level of $p < 0.05$ Wilcoxon test using Bonferroni correction.
* Freidman test.

The effect of AEDs on the immune system has been for recognized a long time.[16] VPA and phenobarbital diminish humoral and cytotoxic T lymphocyte response in mice.[22,23] Suppressor T cells were markedly decreased in the serum of patients treated with phenytoin.[24] Prenatal exposure to diazepam decreased the production of T lymphocytes.[25] However, these studies mostly involve first-generation AEDs. Furthermore, their results are frequently inconsistent and occasionally conflicting.[16] A major source of discrepancy may be in the difficulty of distinguishing the effect of the drugs from the effect of the seizures.[26] Moreover, personal and genetic predisposition, concomitant use of multiple drugs, and drug interactions are other possible additional factors.[16]

There are few data examining the effect of the new AEDs on the immune system. TPM reversed the decrease of in T-lymphocyte proliferation activity induced by the seizure in rats.[27] The purpose of our study was to investigate the effects of one old (VPA) and one new (TPM) drug on the levels of IL-1α, IL1β, IL-6, IL-10 and TNF-α.

The level of IL-1 is very low in the CNS.[19] It has both neurotoxic and neuroprotective effects.[8] Stimuli with a convulsant effect increase the production of IL-1β in microglia-like cells in the hypocampus.[1] Verrotti et al.[14] examined the levels of IL-1α, IL-1β, IL-2, and IL-6 (from peripheral blood mononuclear cells) in 40 patients aged 8.9–16.2 years, treated with VPA and carbamazepine (CBZ) monotherapy and, reported that the group treated with VPA showed statistically significant increase in the levels of IL-1α, IL-1β, and IL-6 and no change in the levels of IL-2, whereas the CBZ group showed an increase in all parameters. In this study, the blood levels of cytokines in 48 healthy children were reported for IL1α, IL-1β, IL-6 as 13.8 ± 1.9 ng/ml, 1.02 ± 0.32 ng/ml and 4.03 ± 1.26 ng/ml, respectively. They did not find a significant differences between the control group and epileptic patients. In our study, the group treated with VPA showed an increase in IL-1α level at the 6th and especially the 12th month of treatment. In our study, although not statistically significant, a VPA-related decrease observed in the level in IL-1β may be significant in terms of the neuroprotective efficacy of VPA.

IL-6 is a pleiotropic cytokine.[1] Although VPA inhibits the production of TNF-α and IL-6 *in vitro*, epileptic patients treated with this drug show increased concentrations of IL-1, IL-6 and IL-5.[14] Verrotti et al.[14] showed increased levels of IL-6, IL-1α and IL-1β with VPA at the 12th month compared to pre-treatment. Shiah et al.[15] gave 1000 mg per day of VPA to 10 healthy male volunteers aged 29.4 ± 10.5 years for 7 days: levels of IL-6 were significantly increased. Kim et al.[28] randomized the patients with bipolar disorder to three groups, and treated 15 patients with VPA, 8 patients with lithium and 8 patients with VPA + lithium. At the beginning of the therapy, they measured the levels of IL-6, IL-4, IL-2, TNF-α, and IFN-γ.

They found significantly higher levels of IL-6 and TNF-α and significantly lower levels of IL-4 in patients compared to the control group. All three groups showed a significant decrease in IL-6 levels at the end of the 6-week therapy compared to baseline.

However, certain other studies have suggested that VPA reduced or did not change the level of IL-6.[5,29,30] In 10 adult patients diagnosed with mania, Maes et al.[29] reported that the plasma levels of IL-6, soluble IL-6 receptor (sIL-6R), soluble IL-2 receptor (sIL-2R) and Transferrin receptor (TfR) remained unchanged following short-term VPA monotherapy, as while De Ponti et al.[5] reported unchanged IL-6 levels under the same conditions. In an experimental study, Ichiyama et al.[30] suggested that VPA acted by inhibiting the production of TNF-α and IL-6 resulting from lipopolysaccharide pathway *via* human monocytic leukemic cells, leading to the activation of NF-κB. Our results showing a non-significant decrease in the levels of IL-6 at the 6th and 12th months in patients treated with VPA do not conflict with the results of Kim and Ichiyama.

TNF-α is a proinflammatory cytokine that shows a neurotropic and neurotoxic effect in the CNS.[18] Animal studies have demonstrated that the levels of TNF-α mRNA were increased after the seizure and returned to basal levels at the end of 3 weeks.[31] Ichiyama et al.[30] showed in *in vitro* models that VPA inhibited the production of TNF-α and IL-6. In the study performed by Kim et al.[28] the levels of TNF-α showed a statistically insignificant decrease following 6-week treatment with VPA, lithium and VPA + lithium.

In our study, TNF-α levels decreased at the 6th month of VPA treatment and returned to baseline levels at 12th month; however, changes were not significant. The results obtained were inadequate to suggest that VPA may show a neuroprotective effect by decreasing the level of TNF-α.

IL-10 is an anti-inflammatory cytokine known as a human cytokine synthesis inhibitor factor (CSIF).[32] IL-10 limits inflammation in the brain. In addition, it accounts for the inhibition of the synthesis of proinflammatory agents, such as interferon-γ (IFN-γ), IL-2, IL-3, TNF-α, and granulocyte macrophage colony-stimulating factor (GM-CSF).[33] In our study, the levels of IL-10 showed a decrease at the 6th and 12th months of treatment compared to the pre-treatment period in both the VPA and TPM groups. However, only the decrease observed at the 6th month compared to baseline was statistically significant in the VPA group. In the group treated with TPM, the levels of IL-10 decreased significantly at the 6th and 12th months.

To our knowledge, no other study has investigated the effect of VPA and TPM on IL-10. The fact that anti-inflammatory cytokine IL-10, with a protective effect, is decreased with the use of VPA and TPM, and together with the observed increased level of IL-1α, suggests a net effect of a proconvulsive type. However, the decrease in IL-1β, IL-6 and TNF-α levels, even if not statistically significant, is a finding that contrasts with the decrease in IL-10. Importantly, other cytokines such as IL-1Ra and IL-2, which were not included in our study might also contribute to the net result.

Another limitation of our study and similar ones in the literature is the lack of clinical correlation: whether the therapeutic effect of AEDs is mediated by their reducing a proconvulsant cytokine or augmenting the synthesis or release of a protective cytokine, and whether the observed changes at 6 or 12 months are related to seizure control are important clinical questions. We could not examine this variable in our study, in which being seizure-free for at least one week was an inclusion criterion by definition.

Differences between studies may be related to the differences in study models (clinical *vs.* experimental), different age groups, and the duration and dosage of AED treatment. Seizures cause changes in cerebral tissue micro-environment, causing the glial cell release of cytokines.[11,12] But some contrasting reports suggest that increased production of cytokines from peripheral blood mononuclear cells was not evident and was not reflect brain cytokine levels.[34,35]

The results of this study demonstrated that VPA and TPM might lead to changes in the levels of cytokines in epileptic patients. However, further studies including blood and CSF cytokine levels with longer and closer follow-up are warranted to interpret the value of these effects in the pathogenesis and treatment of epilepsy, as well as their relation with the systemic immunity of the patient.

Ethical approval

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.'

Conflict of interest

None of the authors has any conflict of interest to disclose.

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References

1. Mlodzikowska-Albrecht J, Steinborn B, Zarowski M. Cytokines, epilepsy and antiepileptic drugs – is there a mutual influence? *Pharmacological Reports* 2007;**59**:129–38.
2. Pacifici R, Paris L, Di Carlo S, Bacosi A, Pichini S, Zuccaro P. Cytokine production in blood mononuclear cells from epileptic patients. *Epilepsia* 1995;**36**:384–7.
3. Anderson P, Moseklide L. Immunoglobulin levels and autoantibodies in epileptics on long term anticonvulsant therapy. *Acta Medica Scandinavica* 1977;**201**:69–74.
4. Garson P, Gonzales-Cornejo S, Roman-Maldonado S, Navorro-Ruiz A. Valproic acid and phenytoin effects on serum proteins and immunoglobulins of epileptic patients. *General Pharmacology* 1985;**16**:411–3.
5. De Ponti F, Lecchini S, Cosentino M, Castelletti CM, Malesci A, Frigo GM. Immunological adverse effects of anticonvulsants. What is their clinical relevance? *Drug Safety* 1993;**8**:235–50.
6. Munoz Fernandez MA, Fresno M. The role of tumour necrosis factor, interleukin 6, interferon-gamma and inducible nitric oxide synthase in the development and pathology of the nervous system. *Progress in Neurobiology* 1998;**56**: 307–40.
7. Vezzani A, Moneta D, Richichi C, Aliprandi M, Burrows SJ. Functional role of inflammatory cytokines and antiinflammatory molecules in seizures and epileptogenesis. *Epilepsia* 2002;**43**:30–5.
8. Beghi E, Shorvon S. Antiepileptic drugs and the immune system. *Epilepsia* 2011;**52**:40–4.
9. Vezzani A, Granata T. Brain inflammation in epilepsy: experimental and clinical evidence. *Epilepsia* 2005;**46**:1724–43.
10. Vezzani A, Conti M, De Luigi A, Ravizza T, Moneta D, Marchesi F, et al. Interleukin-1beta immunoreactivity and microglia are enhanced in the rat hippocampus by focal kainite application: functional evidence for enhancement of electrographic seizures. *Journal of Neuroscience* 1999;**19**: 5054–65.
11. Penkowa M, Molinero A, Carraso J, Hidalgo J. Interleukin-6 deficiency reduces the brain inflammatory response and increases oxidative stress and neurodegeneration after kainic acid-induced seizures. *Neuroscience* 2001;**102**: 805–18.
12. Lehtimaki KA, Keranen T, Palmio J, Makinen R, Hurme M, Honkaniemi J, et al. Increased plasma levels of cytokines after seizures in localization-related epilepsy. *Acta Neurologica Scandinavica* 2007;**116**:226–30.
13. Sinha S, Patil SA, Jayalekshmy V, Satishchandra P. Do cytokines have any role in epilepsy? *Epilepsy Research* 2008;**82**:171–6.
14. Verrotti A, Basciani F, Trotta D, Greco R, Morgese G, Chiarelli F. Effect of anticonvulsant drugs on interleukins-1, -2 and -6 and monocyte-chemoattractant protein1. *Clinical and Experimental Medicine* 2001;**1**:133–6.
15. Shiah IS, Yatham LN, Yeh CB, Ravindran AV. Effect of valproate on plasma levels of interleukin-6 in healthy male humans. *International Clinical Psychopharmacology* 2005;**20**:295–8.
16. Ashrafi M, Hosseini SA, Abolmaali S, Biglari M, Azizi R, Farghadan M. Effect of antiepileptic drugs on serum immunoglobulin levels in children. *Acta Neurologica Belgica* 2010;**110**:65–70.
17. Ichiyama T, Okada K, Lipton JM, Matsubara T, Hayashi T, Furukawa S. Sodium valproate inhibits production of TNF-a and IL-6 and activation of NF-kB. *Brain Research* 2000;**857**:246–51.
18. Li G, Bauer S, Nowak M, Norwood B, Tackenberg B, Rosenow F, et al. Cytokines and epilepsy. *Seizure* 2011;**20**:249–56.
19. Ravizza T, Vezzani A. Status epilepticus induces time dependent neuronal and astrocytic expression of IL-1 receptor type-1 in the rat limbic system. *Neuroscience* 2006;**138**:301–8.
20. Ozkara C, Vigevano R. Immuno and inflammatory therapies in epileptic disorders. *Epilepsia* 2011;**52**:45–51.
21. Marchi N, Granata T, Freri E, Ciusani E, Ragona F, Puvenna V, et al. Efficacy of anti-inflammatory therapy in a model of acute seizures and in a population of pediatric drug resistant epileptics. *PLoS ONE* 2011;**6**(3):e18200. http://dx.doi.org/10.1371/journal.pone.0018200.
22. Oueiroz ML, Mullen PW. Effects of sodium valproate on the immune response. *International Journal of Immunopharmacology* 1992;**14**:1133.
23. Okamoto Y, Shimizu K, Tamura K, Yamada M, Matsui Y, Hayakawa T, et al. Effects of anticonvulsants on cellular immunity. *No to Shinkei Brain and Nerve* 1989;**41**(3):299 [abstract].
24. Başaran N, Kansu E, Hical F. Serum immunoglobulins, complement levels and lymphocyte subpopulations in phenytoin-treated epileptic patients. *Immunopharmacology and Immunotoxicology* 1989;**11**:335–46.
25. Schreiber A, Frei K, Lichtensteiger W, Schlumpf M. The effect of prenatal diazepam exposure on TNF-α production by rat splenocytes. *Agents and Actions* 1993;**38**:265–72.
26. Aronica E, Crino PB. Inflammation in epilepsy: clinical observation. *Epilepsia* 2011;**52**(Suppl. 3):26–32.
27. Kubera M, Budziszewska B, Jaworska-Feil L, Basta-Kaim A, Leśkiewicz M, Tetich M. Effects of topiramate on the kainite-induced status epilepticus, lipid peroxidation and immunoreactivity of rats. *Polish Journal of Pharmacology* 2004;**56**:553–61.
28. Kim Y, Jung H, Myint A, Kim H, Park S. Imbalance between pro-inflammatory and anti-inflammatory cytokines in bipolar disorder. *Journal of Affective Disorders* 2007;**104**:91–5.
29. Maes M, Meltzer HY, Bosmans E, Bergmans R, Vandoolaeghe E, Ranjan R, et al. Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2 and transferrin receptor in major depression. *Journal of Affective Disorders* 1995;**34**:301–9.
30. Ichiyama T, Okada K, Lipton JM, Matsubara T, Hayashi T, Furukawa S. Sodium valproate inhibits production of TNF-a and IL-6 and activation of NF-κB. *Brain Research* 2000;**857**:246–51.

31. Plata-Salaman CR, Ilyin SE, Turrin NP, Gayle D, Flynn MC, Romano witch AE, et al. Kindling modulates the IL-1beta system, TNF-alpha, TGF-beta1, and neuropeptide mRNAs in specific brain regions. *Brain Research Molecular Brain Research* 2000;**75**:248–58.
32. Levin SG, Godukhin OV. Protective effects of interleukin-10 on the development of epileptiform activity evoked by transient episodes of hypoxia in rat hippocampal. *Neuroscience and Behavioral Physiology* 2007;**37**: 467–70.
33. Opp MR, Smith EM, Hughes TK. Interleukin-10 (cytokine synthesis inhibitory factor) acts in the central nervous system of rats to reduce sleep. *Journal of Neuroimmunology* 1995;**60**:165–8.
34. Hulkkonen J, Koskikallio E, Rainesalo S, Keranen T, Hurme M, Peltola J. The balance of inhibitory and excitatory cytokines is differently regulated in vivo and in vitro among therapy resistant epilepsy patients. *Epilepsy Research* 2004;**59**:199–205.
35. Tormoum HY, Badawy NM, Mostafa AA, Harb MY. Plasma interleukin-1beta levels in children with febrile seizures. *Journal of Child Neurology* 2007;**22**:689–92.