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# Resection of the epileptogenic lesion abolishes seizures and reduces inflammatory cytokines of patients with temporal lobe epilepsy

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ABSTRACT

Persistent neuroinflammation is implicated in the pathogenesis of seizures and neuronal degeneration of temporal lobe epilepsy (TLE). Circulating level of inflammatory cytokines was determined during inter-ictal period of 25 non-operated and 10 patients (OP) submitted to anterior temporal lobectomy. OP patients showed marked reduction of IL-1β, TNFα, MIP-1α, but not IL-6 and TGF-β1. Paired analysis done before and after lobectomy showed reduction of inflammatory cytokines but increased TGF-β1 levels, and lack of seizures for more than 6 months. Maintenance of high TGF-β1 and IL-6 cytokines in both groups suggests a role in down-regulation of neuroinflammation and promotion of brain tissue remodeling for neuronal reorganization.



## 1. Introduction

Mesial temporal lobe epilepsy with hippocampal sclerosis (TLE-HS) is a frequent condition within the pharmacoresistant group of epilepsies classified as a syndrome with clinical, electroencephalographic, genetic and immunological features (Berg, 2009; Vezzani et al., 2011). Indication that TLE-HS is a progressive disease was established after evidence that initial precipitant incidents (IPI) in childhood was followed by a latent period until onset of spontaneous seizures at later age (Wieser, 2004). The release of inflammatory cytokines in mesial structures may activate mechanisms associated with prolonged epileptic seizure and neuronal damage (Balosso et al., 2009), and also neurogenesis, neuroplasticity and synaptic reorganization (Jankowsky and Patterson, 2001; Vezzani et al., 2011).

TNF-α proinflammatory cytokine is expressed at low levels in healthy brain but is rapidly upregulated in glia, neurons and endothelial cells during seizures (Fabene et al., 2010). Transient transcription of IL-1β, transforming growth factor beta (TGF-β1) and overexpression of TNFα and IL-6 after induced *status epilepticus* in experimental models (Minami et al., 1991; De Simoni et al., 2000) indicate that activation of cytokine signaling cascade influences development of recurrent seizures and brain tissue remodeling (Lehtimaki et al., 2007; Aronica and Crino, 2011; Lehtimaki et al., 2011). Additionally, altered cytokine plasma levels have been associated with the frequency and severity of temporal seizures, and also with focal and generalized epilepsy during interictal period (Lehtimaki et al., 2007; Mlodzikowska-Albrecht et al., 2007; Alapirtti et al., 2009; Nowak et al., 2011). Such evidences support the hypothesis that dysregulation and/or excessive cytokine production could induce seizures and lead to neuronal degeneration in susceptible subjects. This work aimed to determine the circulating level of cytokines (TNFα; IL-1β; IL-6, sTNFR1, TGF-β1 and CCL3/MIP-1α) that influence inflammatory responses predisposing to seizures and/or tissue remodeling in adult central nervous system. In addition we assessed whether ablation of epileptogenic lesion of TLE patients with hippocampal sclerosis and active pharmacoresistant epilepsy would improve clinical condition and reduce seizures.

## 2. Materials and methods

### 2.1. Patients

This prospective study carried out from October 2009 to December 2010 in the Clementino Fraga Filho University Hospital included after appropriate informed consent, 35 patients with chronic TLE (19 males and 16 females) attending Neurology and Neurosurgery services at a tertiary care university medical hospital. The Hospital Medical Research Ethics Committee and the Brazilian Ministry of Health (CONEP 073-2007) approved this study that complies with the principles laid down in the Declaration of Helsinki. Diagnosis and classification of mesial temporal

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lobe epilepsy with hippocampal sclerosis was based upon previous criteria (Wieser, 2004; Engel, 2006).

Thirty-five patients with medically intractable TLE and hippocampal sclerosis were under investigation for surgery. Among them a group of 10 patients with high (6 to 14 seizures by month) seizure frequency underwent anterior temporal lobe resection and amygdalohippocampectomy (OP). Patients investigated for the history of initial precipitant events (IPI) reported febrile seizure as the most frequent event. At the time of blood collection patients were free from clinical signs of infection and seizure for at least a week, considering that cytokine production is upregulated within 24 h from seizure occurrence (Lehtimaki et al., 2007). Blood samples from OP patients were also collected 48 h before and 8 weeks after surgery. Reference range of plasma cytokines was obtained from 42 (28 males, 66.6%) healthy subjects from the blood transfusion HEMONIT Centre at Fluminense Federal University with age range 18 to 61 years (36.8 ± 9.56 years). Eligibility of control group was assessed by detailed questionnaire, and was only included subjects with no familial history of epilepsy, infectious disease or under use of anti-inflammatory medication.

TLE patients were submitted to a comprehensive investigation and neurological examination which included at least a 4-day video-electroencephalogram (video-EEG) recording, magnetic resonance imaging (MRI), neuropsychological evaluation, and ictal single photon emission computed tomography (SPECT). Latency period was defined as the interval between initial precipitating event (IPI) and the first reported spontaneous epileptic seizure, and silent period as the lag-time between the first seizure and initial clinical evidence of pharmacoresistance (Berg, 2009).

Criteria of eligibility included clinical diagnosis of intractable TLE based on seizure semiology (Luders et al., 1998), ictal video-EEG and 1.5 T MRI of the brain with characteristic image alteration. All patients were good candidates to surgery because they presented unilateral ictal register concordant with unilateral sclerotic hippocampus. Exclusion criteria included occurrence of seizures within the last 24 h before inclusion; concomitant neoplasm; concomitant infectious or inflammatory disease; acute severe cerebrovascular disorder; use of immunomodulatory drug within the last 6 months and/or pregnancy. Also, it was not included patients with genetic syndromes, genetic disorders, cortical dysgenesias, acquired encephalopaties, or autism.

### 2.2. Surgical procedure

Anterior temporal lobe resection and amygdalohippocampectomy were performed in 10 patients by a single neurosurgeon that made consistent measurements of resection parameters during surgery. After surgery, patients continued to use the same antiepileptical drugs (carbamazepine, phenytoin, oxcarbazepine, valproic acid). No neurological and/or cognitive deficits were observed following surgery, and postoperative MRI revealed no further complications.

### 2.3. Blood collection and cytokine assays

5 mL blood samples collected at the same time-matched period (8 a.m. to 10 a.m.) to minimize influence of circadian rhythm in the cytokine release were stored at −80 °C and thawed once just prior cytokine analysis. TNFα, sTNFR1, IL-6, CCL3/MIP-1α and TGF-β1 (R&D-Systems, Minneapolis, MN) and IL-1β (eBioscience, San Diego, CA) were quantified in triplicate by commercial enzyme-linked immunosorbent assays (ELISA) according to the manufacturer's instructions. In 10 patients blood samples were also collected 48 h before and 8 weeks after surgery for comparison of cytokine levels.

### 2.4. Statistical analysis

Statistical analysis was carried out using the GraphPad Prism software (GraphPad Software Inc., San Diego, CA) with tests analyzing differences between groups (Mann–Whitney *U*-test and Wilcoxon signed rank test), differences between OP and nOP were tested with unpaired *t*-test with Welch's correction, one-way ANOVA test with Dunn's Multiple Comparison test for multiple comparisons and Mann Whitney paired test for analysis before and after surgery. The significance level was set to $p<0.05$.

## 3. Results

All patients (n = 35) with temporal lobe epilepsy under investigation for surgery had a characteristic pattern of selective and extensive hippocampal atrophy (Table 1) and were under treatment with anticonvulsant polytherapy medication. In order to accurately define the epileptogenic focus it was performed a careful and detailed clinical semiology including a 4-day video-EEG recording, a 1.5 T MRI, and also single photon emission tomography (SPECT) which indicated that patients had TLE characterized as unilateral ictal mesial temporal lobe epilepsy. During the period of the study, 10 patients (OP) with high (6 to 14) seizure frequency that had been submitted to surgery were seizure-free for more than 6 months whereas 25 patients (nOP) with similar epidemiology but still under clinical investigation for surgery maintained high seizure frequency with 6.5 (range 2 to 12) mean epileptic seizure per month. Such result confirms that sclerotic hippocampus is the main source of electrical events that cause spontaneous epileptic seizures (Spencer, 1998), and emphasize the importance of pre-operative MRI and SPECT for critical selection of patients regarding surgical therapy (Jeha et al., 2006; Vale et al., 2012). Moreover clinical outcome based on Engel classification (Engel, 2006; Vale et al., 2012) indicated that 85% of patients were classified as Engel Class-Ia and 15% Engel Class-Ib as favorable parameter of seizure-freedom outcome for more than 6 months following anterior temporal lobe resection and amygdalohippocampectomy.

In order to establish a possible association of neuroinflammation with this form of epilepsy, we compared TNFα, IL-1β, IL-6 and CCL3/MIP-1α plasma levels between TLE patients (n = 35) and healthy subjects (n = 42). TLE patients showed (Fig. 1) a five-fold increase of

**Table 1**
Demographic characteristics of patients with intractable TLE.
All patients were under treatment with two or more anticonvulsant medications of carbamazepine, phenytoin, oxcarbazepine, and valproic acid. Normal MRI means absence of structural abnormality of brain.

| Characteristics | Operated[a] | Non operated |
|---|---|---|
| | N = 10 | N = 25 |
| Male | 6 (60%) | 13 (52%) |
| Female | 4 (40%) | 12 (48%) |
| Mean age years (range)[a] | 39.8 (27 to 59) | 39.7 (16 to 51) |
| Mean age of seizures at onset | 13 (1 to 35) | 12 (1 to 44) |
| Onset of seizures (*n*) | | |
| ≤18 years | 3 (30%) | 11 (44%) |
| ≥18 years | 7 (70%) | 14 (56%) |
| Mean time of disease duration | 25.5 (6 to 41) | 28 (6 to 50) |
| Course of epilepsy (*n*) | | |
| <10 years | 2 (4 to 8) | 3 (2 to 9) |
| >10 years | 8 (10 to 31) | 22 (11 to 40) |
| Frequency of seizures per month (*n*) | 0 | 6.5 (2 to 12) |
| 3–4 | 0 | 4 (16%) |
| 5–8 | 4 (40%) | 19 (76%) |
| >8 | 6 (60%) | 2 (8%) |
| History of IPI | Present 4 (40%) | Present 7 (28%) |
| Family history of epilepsy (*n*) | | |
| Yes | 2 (20%) | 8 (32%) |
| No | 8 (80%) | 17 (68%) |
| Abnormal MRI (*n*) | 4 (40%) | 7 (28%) |
| TLE (left) | 8 (80%) | 19 (76%) |
| Latency period (median in years) | 22.5 (6 to 35) | 10 (4 to 14) |
| Silent period—(median in years) | 9.87 (0 to 25) | 9.0 (0 to 33) |

[a] Before surgery.

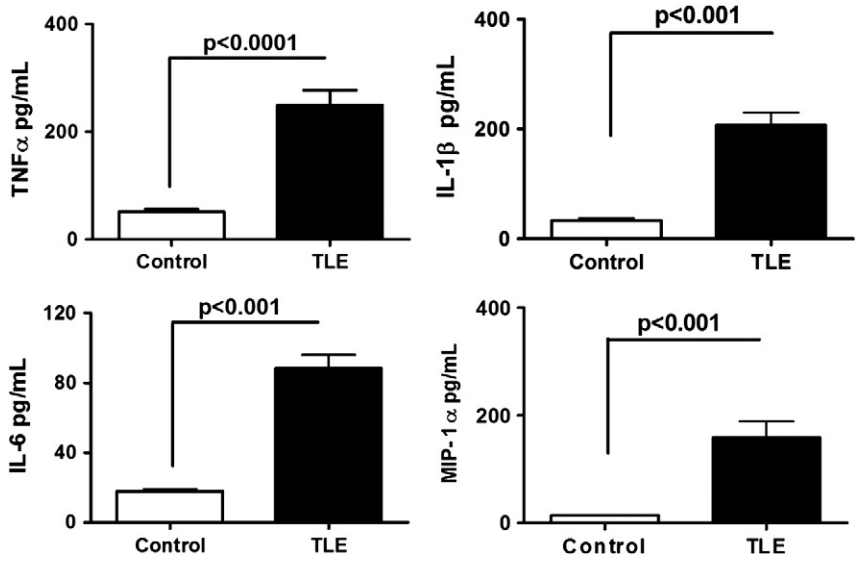


**Fig. 1.** Comparison of cytokines in TLE patients and controls. Results are expressed as mean ± SEM concentration of cytokines in the plasma from control subjects (n = 42) and TLE patients (n = 35) with extensive hippocampal atrophy and under treatment with anticonvulsant medication.

TNFα (249.1 ± 27.9 pg/mL; control: 50.9 ± 5.2 pg/mL), a 6.2 fold increase of IL-1β (207 ± 22.7 pg/mL; control: 33 ± 4.89 pg/mL); a 4.9 fold increase of IL-6 (88.34 ± 7.46 pg/mL; control: 17.89 ± 1.02 pg/mL), and also 11.3 fold increase (158.9 ± 29.49 pg/mL; control: 14,02 ± 1.20 pg/mL) in the levels of CCL3/MIP-1α, a chemoacttractant cytokine to leukocytes, thus confirming the inflammatory characteristics of TLE.

Excessive neuronal activity and production of proinflammatory cytokines have been described in brain tissue after seizures (Hulkkonen et al., 2004). In this context it was important to verify whether surgical resection of compromised area could change plasma level of proinflammatory cytokines in OP patients. In comparison with nOP patients, it was observed (Fig. 2) a significant reduction of TNFα (OP: 149.3 ± 14.75 pg/mL; nOP: 236.1 ± 25.79 pg/mL), IL-1β (OP: 164.1 ± 26.5 pg/mL; nOP: 273.7 ± 33.3 pg/mL); CCL3/MIP-1α (OP: 256 ± 53.23 pg/mL; nOP: 76.80 pg/mL ± 19.17 pg/mL) but IL-6 (OP: 90.29 ± pg/mL; nOP: 79.74 ± 8.59 pg/mL), a neuropoietic cytokine with important role promoting axonal sprouting (Hakkoum et al., 2007). Moreover, repeated analysis in a group of nOP (n = 8) showed maintenance of high cytokine levels, with no significant difference between measurements for IL-1β, IL-6 and MIP-1α (data not shown).

Considering that TNFα effect on seizure threshold depends on endogenous cytokine level within the brain tissue and the type of receptor (sTNFR1) signaling (Figiel, 2008), it was important to determine plasma levels of sTNFR1 receptor. Comparing to control subjects (Fig. 3) a two-tailed analysis showed a significant difference (177.7 ± 8.43; $p < 0.021$) with TLE patients (253.3 ± 24.83) and nOP ($p < 0.01$), but no difference between nOP (223.9 ± 50.2) and OP patients (274 ± 53.7). It was then important to determine the ratio of TNFα and its cognate soluble TNF type I p55 receptor that inhibits TNF-alpha activity but contains a cytoplasmic death domain known to induce apoptosis (Wajant et al., 2003). Loss of balance between the number of ligand bonds of cytokines and the activity of their inhibitors

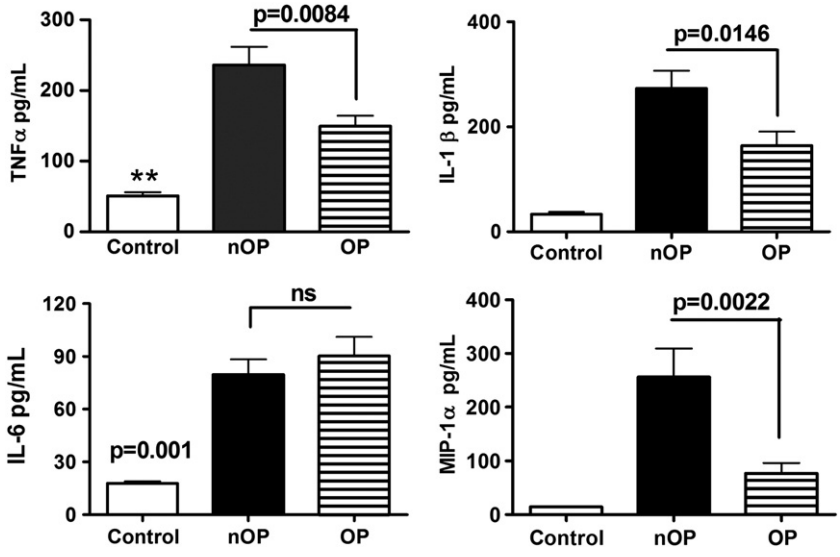


**Fig. 2.** Effect of surgery in plasma levels of inflammatory cytokines. OP (n = 10) patients submitted to surgical resection of epileptogenic lesion by anterior temporal lobe resection and amygdalohippocampectomy and non-operated (nOP = 25). Results are expressed as mean ± SEM.

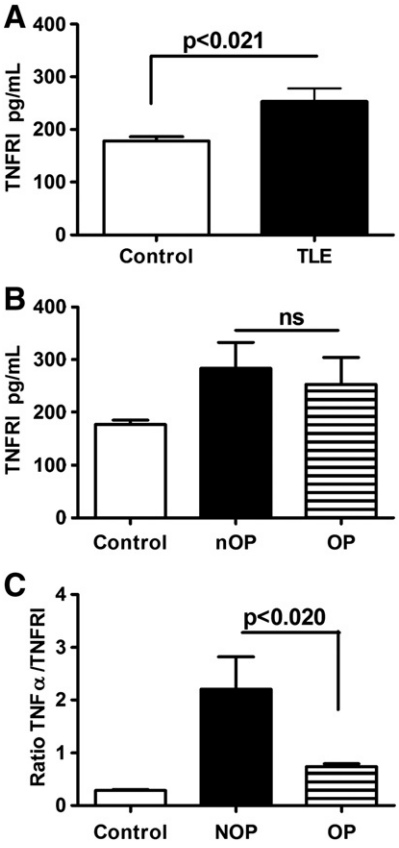


**Fig. 3.** Plasma levels of soluble p55 sTNFR1 and TNFα/TNFR1 ratio. (A) sTNFR plasma levels in control subjects (n = 42) and TLE patients (n = 35), unpaired two-tailed *t*-test showed significant difference $p<0.021$, and also F-test $p<0.0001$ comparing variances between groups; (B) TLE patients (OP n = 10) submitted to surgical resection of epileptogenic lesion by anterior temporal lobe resection and non-operated (nOP) TLE patients (n = 25), no difference (ns) between OP and nOP ($p<0.05$); (C) TNFα/TNFR ratio, the unpaired two-tailed *t*-test with Welch's correction showed significant difference between control and OP ($p<0.0001$) and nOP ($p<0.009$), and also between OP and nOP ($p<0.020$). Results are expressed as mean ± SEM.

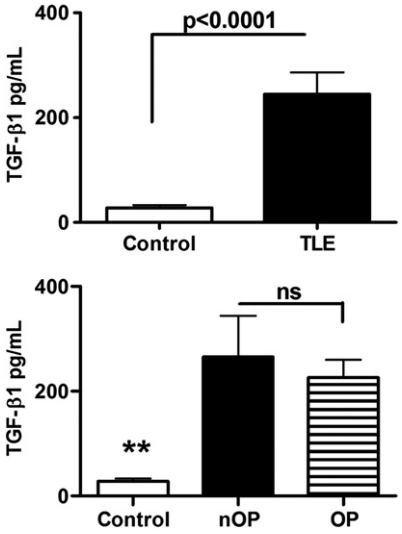


**Fig. 4.** TGF-β1 plasma levels in controls and TLE patients. TGFβ plasma levels in control subjects (n = 42) and TLE patients (OP, n = 10) submitted to surgical resection of epileptogenic lesion and non-operated (nOP) TLE patients (n = 25). Two-tailed unpaired *t*-test with Welch's correction showed significant difference ($p<0.0001$) in plasma levels between control and TLE patients and Kruskal–Wallis test showed significant difference ($p<0.001$) between groups but no difference between nOP and OP ($p<0.05$). Results are expressed as mean ± SEM.

are usually associated with active ongoing inflammation (Thomas, 2001; Veroni et al., 2010). This analysis showed a significant difference ($p<0.001$) of TNF/sTNFR1 ratio between control group (0.28 ± 0.02) and OP patients (0.73 ± 0.05; $p<0.0001$), and also nOP patients (2.20 ± 0.61; $p<0.009$). It was further observed by unpaired two-tailed analysis a significant difference between OP and nOP ($p<0.020$).

Next it was important to determine changes in TGF-β1, a pleiotropic cytokine with diverse actions including regulation of inflammatory response during chronic neurodegeneration and neuronal reorganization (Boche et al., 2006; Wachs et al., 2006). It was observed (Fig. 4) a significant difference ($p<0.0001$) between control subjects (28.18 ± 5.26 pg/mL) and TLE patients: OP (244.8 ± 41.28 pg/mL), and nOP (265.3 ± 78.8 pg/mL), but not ($p>0.05$) between OP and nOP.

We further compared (Fig. 5) the plasma level of proinflammatory cytokines determined 48 h before (BS) and 8 weeks after (AS) surgery. It was observed a marked reduction of IL-1β (BS: 235 ± 53.71 pg/mL; AS:107.5 ± 36.82 pg/mL; $p = 0.0063$); IL-6 (BS: 98.13 ± 9.27 pg/mL; AS: 64.29 ± 6.37 pg/mL; $p = 0.0039$); MIP-1α (BS: 163.9 ± 41.75 pg/mL; AS: 24.96 ± 3.19 pg/mL; $p = 0.0003$), TNFα (BS: 198.6 ± 27.12; AS: 119.14 ± 14.41; $p<0.0258$); TNFR1 (BS: 248.1 ± 40.96; AS: 126.5 ± 13.10; *$p<0.0381$*), but no significant difference of TNFα/sTNFR1 ratio (BS: 1.17 ± 0.28; AS: 0.99 ± 0.12) determined before and after surgery. Conversely, it was observed a significant ($p<0.0149$) increase of TGF-β1 levels between samples collected 48 h before (194.5 ± 11.37 pg/mL) and 8 weeks after surgery (299.7 ± 37.83 pg/mL).

## 4. Discussion

Temporal lobe epilepsy is characterized by focal seizures arising from either the neocortex or mesial temporal structures. Current knowledge from histological analysis of human brain has implicated an ongoing chronic inflammation in the etiopathogenesis of seizures associated with neuronal degeneration and reactive gliosis (Mlodzikowska-Albrecht et al., 2007). Brain parenchymal cells (microglia, astrocytes, and neurons), microvascular cerebral endothelial cells and choroid plexus are known to produce and express cytokine receptors (Aarli, 2000) that may promote neuroinflammation, a process characterized by increased glial activation, pro-inflammatory cytokine production, alteration of blood–brain-barrier permeability, and leukocyte invasion. Yet, peripheral blood cytokines can also enter the brain by passive and/or active transport (Vezzani et al., 2008) thus influencing the pathogenesis of epilepsy as disease-modifying molecules (Bauer et al., 2009). Evidence that TNF receptors are rapidly upregulated in neurons during seizures (Vezzani et al., 2008) is a strong indication that epileptic seizures may trigger abnormal production of pro-inflammatory and proconvulsive cytokines. The present study shows that TLE patients with chronic and medically intractable TLE with ictal mesial temporal lobe hippocampal sclerosis exhibit high IL-1β, IL-6, MIP-1α, TNFα, sTNFR1 and TGF-β1 circulating cytokines in comparison to healthy control subjects. Furthermore, anterior temporal lobe resection and amygdalohippocampectomy was capable to abolish seizures, markedly reduce plasma level of the inflammatory cytokines IL-1β, TNFα, CCL3/MIP-1α but with maintenance of increased IL-6 and TGF-β1 production, both multifunctional cytokines and trophic factors important for promoting neuronal regeneration (Heinrich et al., 2003; Vivien and Ali, 2006; Hakkoum et al., 2007). It is conceivable that reduction of circulating cytokines with neuroinflammatory profile may be used in a long-term follow-up as an additional tool that may be used as an indication of favorable outcome after temporal lobe surgery.

TGF-β1 is a prototypic fibrogenic factor active during tissue remodeling and fibrosis with a central role in brain tissue repair controlling neural stem cell proliferation influenced by changes within the microenvironment (Flood et al., 2001; Vivien and Ali, 2006; Wachs et al., 2006). TGF-β1 is also considered an injury-related cytokine associated with alteration of permeability and vascular integrity of the blood–brain barrier

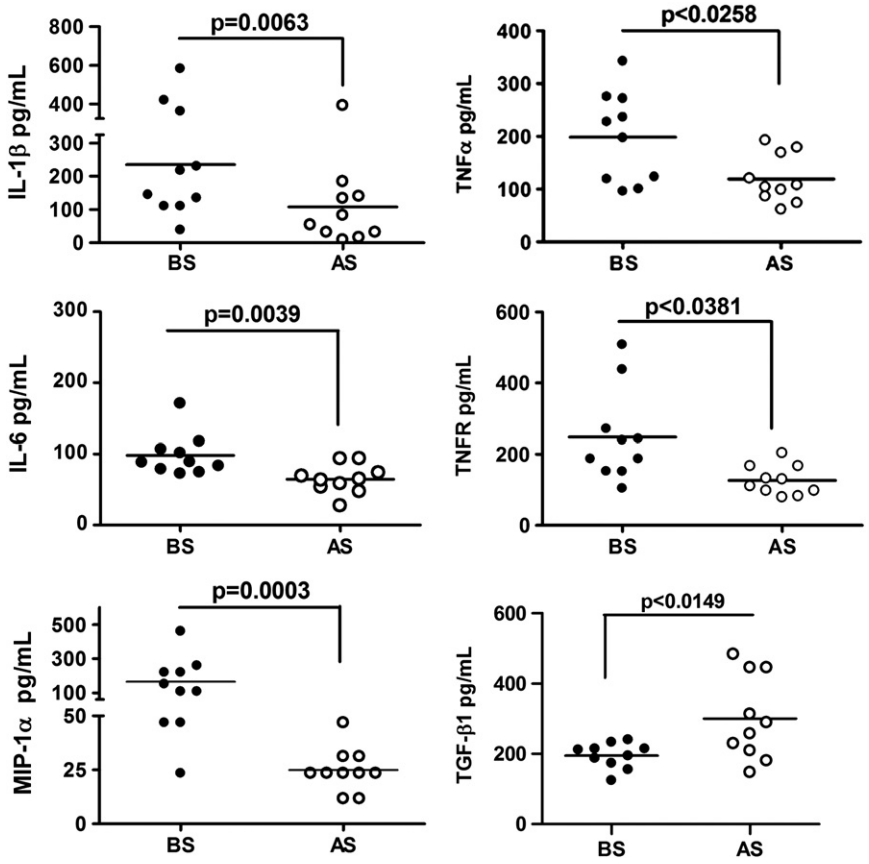


**Fig. 5.** Plasma level of cytokines determined before and after surgery. Plasma level of cytokines determined 48 h before (BS) and 8 weeks after (AS) surgery paired *t*-test analysis showed a significant reduction of IL-1β ($p=0.0063$); IL-6 ($p<0.0039$); MIP-1α ($p=0.0003$); TNFα ($p<0.0258$) and sTNFR1 p55 ($p<0.0381$), but increased TGF-β1 ($p<0.0149$) levels 8 weeks after surgery (AS). Results are expressed as mean ± SEM.

facilitating leukocyte recruitment into the brain tissue and exposure to albumin, thus resulting in gradual development of hypersynchronous neuronal epileptiform activity (Cacheaux et al., 2009; Friedman and Dingledine, 2011). The presence of high TGF-β1 in both groups of TLE patients may reflect sustained tissue remodeling as consequence of neuronal damage associated with seizures in non-operated patients and active neurogenesis in TLE patients that became seizure-free after surgery.

Besides the neurotrophic effect (Mlodzikowska-Albrecht et al., 2007; Figiel, 2008), cytokines may also act as mediators of astrogliosis and neuronal damage associated with seizures (Peltola et al., 2000). Epileptic activity per se is sufficient not only to induce prominent inflammatory response in the brain tissue but also causes seizure-induced neuronal damage and survival (Mlodzikowska-Albrecht et al., 2007; Figiel, 2008). Indeed, TNFα secretion by microglia and sTNFR1 p55 receptor-dependent calcium influx activation cause disturbances in neurotransmitter systems that induces glutamate-dependent neuronal death via activation of the N-methyl-D-aspartate (NMDA) thus leading to clinical seizures (Jara et al., 2007; Mlodzikowska-Albrecht et al., 2007; Vezzani et al., 2008; Cheng et al., 2010). A good clinical outcome may be achieved by complete excision of epileptogenic lesion (Krsek et al., 2007). Indeed the results show that complete excision of epileptogenic lesion abolished seizures up to 6 months after surgery and reduced nearly two-fold the plasma levels of TNFα, IL-1β, MIP-1α.

Some antiepileptic drugs (carbamazepine, valproic acid) inhibit activation of the nuclear transcription factor NFkB which is essential for the production of proinflammatory cytokines (Ichiyama et al., 2000; Mlodzikowska-Albrecht et al., 2007). Since both groups (nOP, OP) were under similar treatment and did not differ in epidemiologic characteristics that might influence cytokine release, the net increase of inflammatory cytokine in nOP patients but not OP patients indicates that the most likely origin of such cytokines is the brain tissue, because surgery markedly reduced cytokine production and abolished seizures only in TLE patients that had undergone anterior temporal lobe resection and amygdalohippocampectomy. The present data also indicate that cytokine levels correlated with seizure frequency and severity (data not shown), thus supporting the hypothesis that inflammation is more extensive when seizures are associated with cell damage (Aarli, 2000; Vezzani et al., 2008). Single seizures cause activation of cytokine cascade and associated inflammatory signals, whereas recurrent seizures cause structural changes and promote brain tissue remodeling (Lehtimaki et al., 2010, 2011). Moreover activated microglia rapidly upregulates TGF-β1 production and signaling which induces epileptiform activity, but may conversely down regulates microglial responses and minimize brain inflammation (Boche et al., 2006; Wachs et al., 2006; Cacheaux et al., 2009). It is not ruled out that as already proposed (Lu et al., 2009), sustained production of TGF-β1 in both OP and nOP patients is modifying the glial–neuron interaction during epileptogenesis and/or exerting a cytoprotective activity and tissue repair. High production of TGF-β1 and IL-6 in both groups indicates a central role in sustained tissue remodeling (Peltola et al., 2000; Heinrich et al., 2003; Vivien and Ali, 2006; Hakkoum et al., 2007) associated with detrimental signaling as consequence of neuronal damage associated with recurrent seizures in epileptic tissue (non-operated patients), but conversely due to activation of newly neuronal–glial circuitry reorganization in patients that became seizure-free after surgery.

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