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ORIGINAL ARTICLE

Is there a Difference between Typical and Atypical Hippocampal Sclerosis Regarding Pre-Operative Blood Inflammatory Markers?

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Abstract

Introduction: The purpose of this retrospective study was to provide whether there was a difference regarding pre-operative inflammatory markers between typical and atypical hippocampal sclerosis (HS).

Methods: For this purpose, 44 patients who underwent epilepsy surgery due to drug-resistant temporal lobe epilepsy were included. Pre-operative neutrophil, lymphocyte, monocyte, and platelet counts as well as neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, lymphocyte-monocyte ratio, and systemic immune-inflammation index) were noted from peripheral blood tests.

Results: Although the majority of inflammatory markers showed higher levels in typical HS, no significant differences were found. None of the markers studied showed a correlation with the degree of neuronal loss.

Discussion and Conclusion: Although no differences between typical and atypical HS were demonstrated, there was a trend to increase in the levels of some inflammatory markers in typical HS which is severe form of neuronal loss compared to atypical HS and further studies with larger cohort of retrospective and preferably prospective are needed.

Keywords: Epilepsy; hippocampal sclerosis; inflammation; inflammatory marker; temporal lobe epilepsy.

Temporal lobe epilepsy (TLE) related to hippocampal sclerosis (HS) is the most common form of focal epilepsy which affects people worldwide. Medical treatment with anti-epileptic drugs (AED) is the first line of treatment but they can lower seizure frequency for a limited period of time because of developing drug resistance. For this reason, surgical resections generally are performed which leads to good seizure outcome with high rate of seizure freedom[1,2] and increases quality of life[3]. The pathophysiological mechanism(s) behind development and progression of TLE is poorly understood and some patients still have seizure even after a good surgical resection of the temporal lobe. This unwanted clinical situation has partly been explained due to that fact that HS is generally associated with temporal neocortical pathology such as focal cortical dysplasia[2]. Thus, the term temporal lobe sclerosis has been used by some[4].

Over the past 10 years, experimental[5] and clinical stud-

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ies[6,7] have shown that inflammation may have a central role in the progression of TLE, but there has been no common consensus that whether inflammation is a cause or consequence. Leukocyte or lymphocyte and monocyte infiltration of the hippocampus and temporal cortex have been demonstrated in animal model of TLE[5,8] and human tissues resected from the temporal lobe as well[6,9]. More important, increased expression and elevated levels of cytokines, the central players in inflammation, and chemokines in both peripheral blood and cerebrospinal fluid of patients with TLE suggested that local and systemic inflammatory processes may take place in epileptogenesis[10,11]. In animal models of status epilepticus and patients with epilepsy, increased numbers of lymphocytes, especially CD4 T lymphocytes underscores the presence of chronic inflammation in epileptic tissue[5,6,12].

Recently, clinical studies including glioma showed that chronic inflammation which is now regarded as one of the hallmarks of cancer can be detected using simple, effective and cheap blood tests, complete blood count (CBC)[13-16]. They underline that neuro-inflammation plays a central role in development of progression of cancers, including glioma and blood levels of some inflammatory markers, such as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), and systemic immune-inflammation index (SII) can be used for differentiation of low and high-grade gliomas and more importantly for detection of tumor progression. It is clearly demonstrated that high NLR, PLR or SII and low LMR indicated high grade gliomas.

With the same sense, TLE is a chronic neurological disorder and inflammatory reactions involving in pathogenesis of TLE can have a systemic reflection measurable in peripheral blood. Analyzing blood parameters in epilepsy surprisingly was less studied,[17-21] and peripheral inflammatory markers studied in gliomas have not been evaluated in epilepsy. A few clinical studies including children with different epilepsy syndromes reported hemogram parameters[21] and some others tried to propose useful marker such as mean platelet volume (MPV)[17] or NLR as a marker of differentiation of simple and complex febrile seizures (CFS)[18]. Unfortunately, there has been no common consensus on which marker is the best in epilepsy.

In this retrospective analysis of patients with TLE underwent surgical resection, we tried to share our results with respect to pre-operative inflammatory markers in typical and atypical HS proven by pathological examinations. Our hypothesis was that since TLE is a chronic inflammatory disorder, there may be a change in the levels of inflammatory markers that can be detected systemically from the peripheral blood analysis. Moreover, there may be a difference between typical (International League Against Epilepsy [ILAE] type-I) and atypical ILAE (type II and III) HS regarding pre-operative blood inflammatory markers, the severe the HS (ILAE type Ia or Ib), the higher the level of pre-operative inflammatory markers should be in peripheral blood analysis.

Materials and Methods

Patients, Surgical Procedure and Systemic Inflammatory Markers

After a long discussion at our local epilepsy meeting, every data including clinical semiology, electrophysiology such as scalp and invasive electroencephalography if needed, radiological examinations including positron emission tomography was evaluated. After obtained informed consent from every patient, anterior temporal resections were performed. As soon as hospitalization for surgery, CBC as a routine laboratory tests before surgery was taken and pre-operative inflammatory markers were studied. Here, neutrophil, platelet, and monocyte counts (10^3 mm^3) were recorded. (NLR: absolute neutrophil count divided by absolute lymphocyte count), (PLR: absolute platelet count divided by absolute lymphocyte count), LMR (absolute lymphocyte count divided by absolute monocyte count), and[22] (SII: absolute platelet count x NLR) were calculated and noted as pre-operative inflammatory markers.

Inclusion Criterias and Subtypes of HS

The inclusion criteria for this study were as follows: (1) HS verified and graded according to the ILAE[23] by histopathology study, (2) no chemotherapy, radiotherapy and steroid use before surgery, (3) no co-morbidities or extracranial tumor or infection, (4) no previous surgery because of any other epilepsy syndromes, (5) presence of CBC before surgery, (6) completed informed consent, and (7) patient at least 18 or more years old. Subtypes of HS were defined by ILAE[23] as follows: Typical HS (type-I) was subdivided into type-Ia (neuronal loss limited to the cornu ammonis [CA]1, CA3, and CA4) and type-Ib (severe from in which neuronal loss throughout hippocampus-CA1, CA2, CA3, and CA4). Atypical HS included type-II (neuronal loss within CA1), and type-III (neuronal loss limited to CA4 or end folium). Neuronal loss in every hippocampal subfield, namely CA, was divided into severe, moderate, and mild neuronal loss.

Statistical Analysis

Statistical analysis was performed using SPSS version 22.0. Results were reported here as mean±standard deviation. Independent samples t-test and Chi-square test were used in appropriate comparisons. Correlation analysis was judged by Pearson correlation coefficient test. A probability value ($p<0.05$) was considered statistically significant.

Results

This retrospective analysis consisted of a total of 44 patients who underwent surgery due to drug-resistant TLE. The group included 23 males (52.3%) and 21 females (47.7%) with a mean age of at the time of surgery 31.68±9.68 years. No significant difference was observed between gender ($p=0.76$; χ^2 test). Right and left-sided temporal resections were 20 (45.5%) and 24 (54.5%), respectively. Again no significant difference was found with respect to side of surgery ($p=0.54$; χ^2 test). Histopathological examinations revealed that ILAE subtypes of HS were as follows: 12 in Ia (27.3%), 25 in Ib (56.8%), 5 in II (11.4%), and 2 in III (4.5%). When typical and atypical groups were considered, we had 37 patients (84.1 %) in typical HS (type-I: Ia + Ib) and 7 patients (11.4 %) in atypical (type-II + III) HS.

In 42 patients, neuronal loss was detected in CA1 subfield. Severe neuronal loss (38 patients; 90.5%) was the most common followed by moderate (3 patients; 7.1%) and mild neuronal loss (1 patient; 2.4%). Neuronal loss was noted in CA2 subfield of hippocampus in 23 patients which was as follows: Severe in 3 (13%), moderate in 4 (17.4%), and mild in 16 (69.6%) patients. A total of 37 patients showed neuronal loss in CA3 in which we had severe, moderate, and mild neuronal loss in 14 (37.8%), 10 (27%), and 13 (35.1%), respectively. In CA4 we had severe neuronal loss in 18 (46.2%), moderate neuronal loss in 6 (15.4%), and mild neuronal loss in 15 (38.5%) patients. Statistical comparisons among the subfield of the hippocampus regarding neuronal loss showed significant differences between CA1 and CA2 ($p=0.001$) and between CA3 and CA4 ($p=0.00001$).

Table 1 summarizes levels of pre-operative inflammatory markers in peripheral blood in every ILAE subtypes of HS. There was a trend to decrease in both neutrophil and monocyte counts from subtype Ia to II. However; lymphocyte and platelet counts increased in the most severe form of HS, namely subtype Ib. Levels of NLR, PLR, and SII showed a decline from subtype Ia to II but LMR showed trend to increase from subtype Ia to II. We did not consider subtype III because of very less number included in this group (n=2) when evaluating the trend. Statistical comparisons of all ILAE subtypes with each other did not show significant differences regarding the blood levels of pre-operative inflammatory markers mentioned in Table 1 ($p>0.05$).

Table 2 shows pre-operative inflammatory markers in typ-

Table 2. Pre-operative inflammatory markers in typical and atypical hippocampal sclerosis

Marker	Typical HS (n=37)	Atypical HS (n=7)	p
Neutrophils	3.65±1.38	3.70±1.45	0.92
Lymphocytes	1.94±0.58	1.88±0.51	0.77
Monocytes	0.50±0.15	0.39±0.10	0.08
Platelets	240.98±61.70	222.20±29.83	0.43
NLR	2.02±0.96	2.05±0.81	0.93
PLR	133.01±49.03	126.69±31.20	0.74
LMR	4.27±1.93	5.24±2.68	0.26
SII	497.48±298.37	444.98±150.58	0.65

HS: Hippocampal sclerosis; LMR: Lymphocyte-monocyte ratio; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; SII: Systemic immune-inflammation index.

Table 1. Pre-operative inflammatory markers according to subtypes of hippocampal sclerosis

Marker	Ia (n=12)	Ib (n=25)	II (n=5)	III (n=2)
Neutrophils	3.80±0.77	3.57±1.60	3.16±1.10	5.04±1.66
Lymphocytes	1.85±0.49	1.99±0.63	1.81±0.53	2.04±0.60
Monocytes	0.52±0.17	0.49±0.15	0.37±0.11	0.42±0.10
Platelets	231.58±66.14	245.49±60.34	224.88±29.95	215.50±40.30
NLR	2.19±0.69	1.93±1.07	1.89±0.93	2.44±0.09
PLR	134.15±56.38	132.46±46.35	130.55±28.84	117.04±47.46
LMR	3.79±1.26	4.51±2.17	5.42±3.26	4.78±0.22
SII	513.28±236.98	489.89±328.05	412.96±167.26	525.04±78.73

LMR: Lymphocyte-monocyte ratio; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; SII: Systemic immune-inflammation index.

ical (type-I: subtype Ia and Ib) and atypical (type-II and III) forms of HS. In typical HS group, lymphocyte, monocyte, and platelet counts were higher than atypical HS group but neutrophil count was lower in typical HS group. No significant difference was found between the two groups (p>0.05). In typical HS group PLR and SII were higher and NLR and LMR were lower compared to atypical HS group. Again the differences did not reach significant level between the two groups (p>0.05).

Figures 1 and 2 show results of correlation analysis between pre-operative inflammatory markers. A strong positive correlations were found between NLR and PLR (r=0.58, p=0.00001), NLR and SII (r=0.86, p=0.00001), and PLR and SII (r=0.75, p=0.00001). However, strong negative correlations were found between NLR and LMR (r=-0.52, p=0.00001), PLR and LMR (r=–0.55, p=0.00001), and LMR and SII (r=–0.46, p=0.001). There was no significant association between none of the pre-operative inflammatory markers and the ILAE subtype of HS (p>0.05).

Discussion

It is difficult to compare and discuss our results with the current literature because of lack of study like the present one reporting hemogram parameters in patients with TLE. We, for the 1st time, tried to provide pre-operative inflammatory markers which extensively studied in cancer including brain gliomas, in TLE. There are very limited numbers of reports including children with epilepsy showed conflicting results[17-20]. Some proposed MPV as a marker of differentiating simple febrile seizure from CFS[17] but some others showed the reverse[19]. Moreover, NLR and red cell distribution width levels were found to be higher in children with CFS compared to SFS and could produce clear cut distinction in Goksugur et al.,[18] but not in Yigit et al.,[19] In a recent study by Eroglu et al.,[21] showed that neutrophil and lymphocyte counts were significantly higher in patients with epilepsy during seizure but lower during seizure-free period compared to healthy controls. In the same study, they found NLR was not significantly different in patients with epilepsy and controls. However, above mentioned

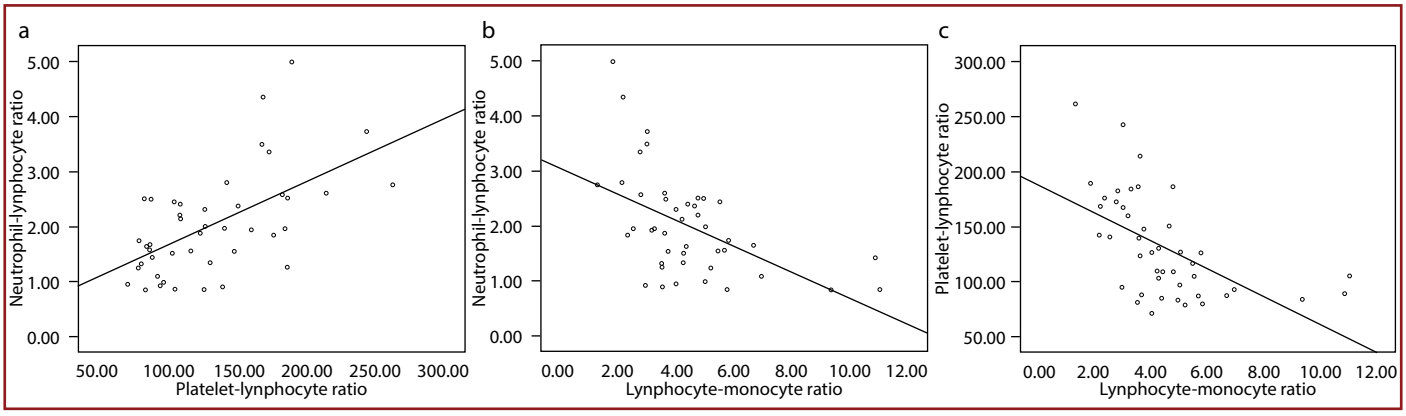

Figure 1. Correlation analysis demonstrating a strong positive interaction between neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) **(a)** but negative correlations between NLR and LMR **(b)**, between PLR and LMR **(c)**.

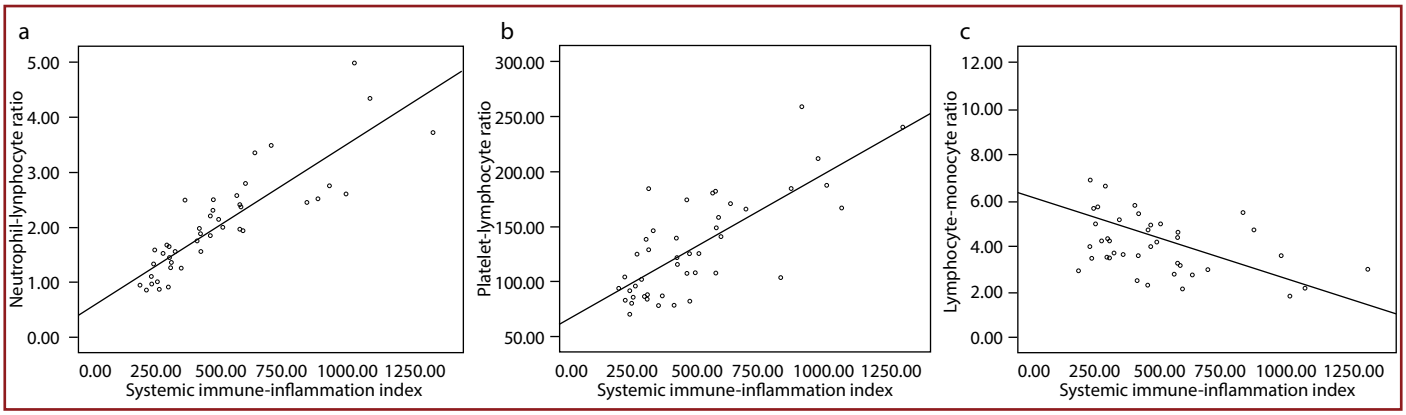

Figure 2. A strong positive correlations were recorded between neutrophil-lymphocyte ratio (NLR) and SII **(a)** and between platelet-lymphocyte ratio and SII **(b)**. However, LMR showed a negative correlation with SII **(c)**.

studies did not include homogeneous patient groups and the majority focused on febrile seizure in children.

We have a chance to discuss and compare our results with clinical studies that have included low and high grade glioma in which inflammation has been proven to play a crucial role in both development of progression of glioma[13-16]. The common finding was that neutrophil and monocyte counts increased but lymphocyte and platelet counts decreased as the tumor grade increased. Furthermore, NLR, PLR and SII significantly increased but LMR significantly decreased in patients with high-grade gliomas. They supported that high NLR; especially ≥4 shows progression of glioma grade and is a poor prognostic sign. Lower level of LMR was found in patients with glioma compared to non-lesional epilepsy and the study suggested that LMR may be useful biomarker for the differentiation of glioma from other intracranial diseases including non-lesional epilepsy[14]. Neutrophilia and lymphopenia are common findings in tumorigenesis and the underlying mechanism has been poorly understood. Some authors[24,25] suggested that cytokines and chemokines secreted by glioma may stimulate neutrophil production that causes increase neutrophil infiltration around tumor microenvironment and increase count in peripheral blood. Increased neutrophil may also be due to increased production of reactive oxygen species by tumor cells[26]. Increased neutrophil levels can inhibit lymphocyte activity and stimulate lymphocyte apoptosis.

We can apply the above mentioned scenario taking place in tumor inflammation to chronic epilepsy such as TLE, because basic inflammatory cells have been found to be the same in TLE. Chronic inflammatory infiltrate has been documented either in the hippocampus and the temporal cortex in both experimental models of seizure[5,8] and clinical cases of TLE[6,9]. The cell populations were mainly of lymphocytes predominantly CD4+ T cells and a small numbers of CD8+ T cells and B cells. It is still unclear whether inflammation is a cause or a consequence of ongoing seizure in TLE but experimental studies suggest inflammation may promote epileptogenesis by several ways such as microglial activation, neuronal loss, or disruption of the blood-brain barrier[10,11]. The role played by inflammation in TLE has been strengthened by animal studies in which blockade of proinflammatory pathways reduces seizure frequency and duration[27].

Our results did not support our hypothesis that pre-operative inflammatory markers did not show expected increase in severe HS such as ILAE subtype type-Ib HS. However, globally we had similar results supporting the studies including gliomas that neutrophil and monocyte counts, NLR, PLR, and SII showed a trend to decrease and LMR showed a trend to increase from type-II to type-II (from severe to moderate/mild neuronal loss). Unexpectedly, our results demonstrated lower levels of neutrophil but higher levels of lymphocyte, monocyte, and platelet counts in typical HS patients. In typical HS group, PLR and SII were higher but NLR and LMR were lower. These findings may suggest that inflammatory cells may play a role in different manner compared to glioma cells or TLE is a chronic disorder and almost all patients were on AED for a long time which may have affected the cell counts[28]. Furthermore, since we had blood analysis during seizure-free period (at the time of hospital admission) before surgery, the unexpected cell counts would have been obtained. No significant differences were found between ILAE subtypes of HS regarding pre-operative inflammatory markers. This result is in line with a recent study which showed that no significant association between the presence of a chronic inflammatory infiltrate within hippocampal tissue and ILAE subtype of HS[6].

Study Limitations

The authors who contributed to this retrospective analysis of patients with TLE are aware of some limitations. First, this is a retrospective analysis of data and some bias may have occurred during data retrieval. Second, patients with TLE use AED for long-term so that cell counts may have been affected by such drugs and third larger patient cohort is needed to provide more comprehensive results.

Conclusion

Although the present study did not show significant difference between ILAE subtype of typical and atypical HS regarding pre-operative inflammatory markers in patients with TLE, the results are preliminary and may give an idea for further studies. As we have more data related to inflammation and inflammatory cells in patients with TLE, we will be able to develop new therapeutic approaches in addition to surgical resections.

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