Background: Blood brain barrier (BBB) permeability plays an important role in the brain impairments. The barrier is composed of endothelium cells, due to the presence of tight junctions that connect endothelium cells. The failure of BBB function has triggering chronic or acute seizures through brain inflammation and BBB permeability. Seizure induces vasodilation, BBB leakage and up-regulation of vascular cell adhesion molecules which able to bind integrins blood leukocytes.

Materials and Methods: In this case-control study we included 40 epileptic patients who were sampled during a seizure as a case group and 20 healthy subjects as a healthy control group. Plasma levels of the inflammation and endothelium markers including intercellular adhesion molecule (ICAM), vascular adhesion molecule (VCAM), interleukin 1 beta (IL-1β) and C-reactive protein (CRP) were measured by enzyme-linked immunosorbent assays (ELISAs).

Results: The ICAM and VCAM concentration in the epileptic patients (135.8 ± 5.35) (52.04 ± 4.24) were significantly higher than healthy control group (110.32 ± 5.04) (23.38 ± 3.01) (P < 0.005). IL-1 beta concentration was not significantly different between groups (P = 0.594). However, CRP level was significantly up-regulated in epileptic patients (P < 0.005).

Conclusion: Epileptic patients have BBB leakage and dysfunction as the up-regulation of the endothelium cytokines showed. The BBB leakage may be the result of the inflammatory impairment.

Key Words: Endothelium, epileptic, Inflammation

INTRODUCTION

Due to its unique structure, the blood-brain barrier (BBB) permeability plays an important role in the brain impairments. The barrier is composed of endothelium cells, due to the presence of tight junctions that connect endothelium cells. The failure of BBB function has triggering chronic or acute seizures through brain inflammation and BBB permeability. Blood vessels in the brain can respond to the electrical activity due to seizure, causing either transient hyperperfusion in healthy tissue or severe hypoperfusion in tissue at risk of progressive damage. Epilepsy could be resulted of the inflammatory response and the endothelium

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Brain inflammation and increased level of IL-1β was found after the seizure has been detected in the post-epileptic animal model. Inflammation and endothelium dysfunction and BBB leakage in epileptic patients might be the reason of endothelium dysfunction and BBB leakage in epileptic patients.

Seizure induces vasodilation, BBB leakage and up-regulation of vascular cell adhesion molecules which able to bind integrins blood leukocytes. An acute induced seizure associated with vascular leakage which was prevented by inhibiting leukocyte-vascular adhesion, which could linked to vascular damage. Chronic expression of VCAM after seizure suggests that leukocyte-vascular interactions may continue, contributing to BBB permeability and brain damage. To the best of our knowledge, there are rare study showed BBB dysfunction including endothelium factors and inflammation response together in epileptic patients versus none epileptic patients. Therefore we aimed to evaluate the serum concentration of endothelium and inflammatory cytokines in epileptic patients versus none epileptic patients.

MATERIALS AND METHODS

This case-control study has been performed in January to March 2012 to evaluate the hypothesis that epileptic patients have BBB dysfunction and leakage. The study was conducted in Ayatollah Kashani and Alzahra hospital, Isfahan, Iran over the 40 epileptic patients as the case group and 20 healthy control people as a control group. All the patients were checked for other diseases, which can effect on the serum level of inflammation cytokines such as a rheumatologic disease, diabetes mellitus (DM) and history of allergy. Epileptic patents were defined as age more than 16 years, idiopathic epilepsy, starting epilepsy at least in the last 6 months. Patients with a disease which can effect on the serum level of inflammation cytokines symptomatic epilepsy, history of trauma, stroke, metabolic disorder, metabolic syndrome, smoking and drug abuser were excluded from the study.

Blood sampling
This study was approved in local ethic committee of Isfahan University of Medical Sciences and all patients and control signed a consent form.

Blood was sampled at the seizure-free period of epileptic patients. Five milliliters of venous blood was drawn from each participant and immediately centrifuged. Serum samples were then frozen and kept at -70°C.

Plasma samples were thawed and further processed according to manufacturer’s instructions. ICAM, VCAM, IL-1β and CRP concentrations in plasma were quantified by enzyme-linked immunosorbent assay.

Statistics
Data have been analyzed by using SPSS 18 and are presented as mean values ± standard deviation. Plasma concentrations (ICAM, VCAM, IL-1β and CRP) between groups were statistically assessed Kruskal-Wallis one-way analysis of variance on ranks followed by Dunn’s post hoc test for variable group sizes. The Pearson Chi-square test or Fisher’s exact test was used for comparing the individual variables between groups. P < 0.05 was taken as statistically significant.

RESULTS

Participants
Forty epileptic patients had been included as the case group and 20 non-epileptic people as the control group. About 30 patients were excluded because of the reason of their seizures (e.g., Head trauma, drug using, pseudo-epilepsy). Baseline characteristic (sex and age) as Table 1 shows were not significantly different between groups.

Descriptive data
The groups contain 20 (50%) and 12 (60%) male subjects respectively. The means (±standard error) of age in each group were 30.48 ± 2.03 and 27.35 ± 3.42 respectively [Table 1].

Main results
Table 2 shows mean levels of serum concentration of ICAM, VCAM, IL-1β and CRP in each group; ICAM and VCAM serum concentration, as endothelium cytokines, were investigated in epileptic patients and non-epileptic control group. There were significant
**Table 1: Baseline characteristics**

| Variables              | Epileptic patients | Nonepileptic subjects | \( P \) |
|------------------------|--------------------|------------------------|--------|
| Sex (male) (%)         | 20 (50)            | 12 (60)                | 0.473  |
| Age (mean±SE)          | 30.48±2.03         | 27.35±3.42             | 0.409  |

SE: Standard error

Table 2: The relation between endothelium and inflammatory cytokines in epileptic patients and nonepileptic people

| Variables* | ICAM | VCAM | IL-1β | CRP |
|------------|------|------|-------|-----|
| Epileptic patients | 135.8±5.35 | 52.04±4.24 | 15.59±0.75 | 52.42±7.58 |
| Nonepileptic subjects | 110.32±5.04 | 23.38±3.01 | 16.27±0.96 | 28.09±5.95 |

\( P \) values <0.05 was taken as statistically significant

**DISCUSSION**

The results revealed significant higher serum concentrations of ICAM and VCAM in epileptic patients versus non-epileptic people. Furthermore, two inflammatory cytokines, IL-1β and CRP were measured. Serum concentration of CRP were significantly different between groups (\( P = 0.04 \)). However, serum concentration of IL-1β was not significantly different (\( P = 0.594 \)). Although serum concentration of CRP were significantly different between the two groups (\( P = 0.04 \)), the serum concentration of IL-1β was not significantly different (\( P = 0.594 \)).

**Inflammation response**

The results showed significant higher serum concentration of CRP in epileptic patients in contrast with non-epileptic people but serum concentration of IL-1β was not significantly different between these groups. Other study showed IL-1β had a direct effect on BBB permeability and lowers the seizure threshold and promotes epileptogenesis on-the-spot.\(^{[21]}\) However, IL-1β up-regulates in the acute phase of the seizure. The current study evaluated the patients in inter-ictal phase; therefore IL-1β did not significantly different between groups. In contrast the CRP that up-regulated in inter-ictal phase were significantly higher in epileptic patients. CRP participates in brain ischemia, stroke, vascular events and act as a chronic inflammatory cytokine. Previous studies investigated CRP baseline concentration in epileptic patients. They showed that CRP baseline concentration was higher in epileptic patients versus non-epileptic people.\(^{[22,23]}\) Higher baseline CRP levels were also detected in those with older age at diagnosis. In addition, CRP level was higher in elder participants than in youngsters in control group.\(^{[24]}\)

**Limitation**

Small sample size should have been considered as a limitation of this study.

**CONCLUSION**

The endothelium mediators (ICAM and VCAM) were higher in epileptic patients may show BBB dysfunction in epileptic patients. From the inflammatory cytokines; CRP was higher in epileptic patients in inter-ictal phase and IL-1b had no significant level in epileptic patients in inter-ictal phase.

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**Conflicts of interest**

There are no conflicts of interest.
REFERENCES

1. Ivens S, Gabriel S, Greenberg G, Friedman A, Shelef I. Blood-brain barrier breakdown as a novel mechanism underlying cerebral hyperperfusion syndrome. J Neurol 2010;257:615-20.

2. Oby E, Janigr D. The blood-brain barrier and epilepsy. Epilepsia 2006;47:1761-74.

3. Dreier JP. The role of spreading depression, spreading depolarization and spreading ischemia in neurological disease. Nat Med 2011;17:439-47.

4. Winkler MK, Chassidim Y, Lublinsky S, Revankar GS, Major S, Kang EJ, et al. Impaired neurovascular coupling to ictal epileptic activity and spreading depolarization in a patient with subarachnoid hemorrhage: Possible link to blood-brain barrier dysfunction. Epilepsia 2012;53 Suppl 6:22-30.

5. Vezzani A, French J, Bartfai T, Baram TZ. The role of inflammation in epilepsy. Nat Rev Neurol 2011;7:31-40.

6. Vezzani A, Aronica E, Mazarati A, Pittman QJ. Epilepsy and brain inflammation. Epilepsia 2012;53 Suppl 6:37-44.

7. Kim SY, Buckwalter M, Soreq H, Vezzani A, Kaufer D. Blood-brain barrier dysfunction-induced inflammatory signaling in brain pathology and epileptogenesis. Epilepsia 2012;53 Suppl 6:37-44.

8. Fabene PF, Navarro Mora G, Martinello M, Rossi B, Mergo F, Ottoboni L, et al. A role for leukocyte-endothelial adhesion mechanisms in epilepsy. Nat Med 2008;14:1377-81.

9. Zattoni M, Mura ML, Deprez F, Schwendener RA, Engelhardt B, Frei K, et al. Brain infiltration of leukocytes contributes to the pathophysiology of temporal lobe epilepsy. J Neurosci 2011;31:4037-50.

10. Marchi N, Oby E, Batra A, Uva L, De Curtis M, Hernandez N, et al. In vivo and in vitro effects of pilocarpine: Relevance to ictogenesis. Epilepsia 2007;48:1934-46.

11. Marchi N, Johnson AJ, Puvenna V, Johnson HL, Tierney W, Ghosh C, et al. Modulation of peripheral cytotoxic cells and ictogenesis in a model of seizures. Epilepsia 2011;52:1627-34.

12. Holtman L, van Vliet EA, Aronica E, Wouters D, Wadman WJ, Gorter JA. Blood plasma inflammation markers during epileptogenesis in post-status epilepticus rat model for temporal lobe epilepsy. Epilepsia 2013;54:589-95.

13. Lehtimäki KA, Keränen T, Palmio J, Mäkinen R, Hurme M, Honkanen N, Holappa S, et al. Increased plasma levels of cytokines after seizures in localization-related epilepsy. Acta Neurol Scand 2007;116:226-30.

14. Alapitti T, Rinta S, Huikkonen J, Mäkinen R, Keränen T, Peltola J, Interleukin-6, interleukin-1 receptor antagonist and interleukin-1beta production in patients with focal epilepsy: A video-EEG study. J Neurol Sci 2009;280:94-7.

15. Tuttolomondo A, Di Sciacca R, Di Raimondo D, Renda C, Pinto A, Licata G. Inflammation as a therapeutic target in acute ischemic stroke treatment. Curr Top Med Chem 2009;9:1240-60.

16. Librizzi L, Regondi MC, Pastori C, Frigerio S, Frasconi C, de Curtis M. Expression of adhesion factors induced by epileptiform activity in the endothelium of the isolated guinea pig brain in vitro. Epilepsia 2007;48:743-51.

17. Eid T, Brines ML, Cerami A, Spencer DD, Kim JH, Schweitzer JS, et al. Increased expression of erythropoietin receptor on blood vessels in the human epileptogenic hippocampus with sclerosis. J Neuropathol Exp Neurol 2004;63:73-83.

18. Seiffert E, Dreier JP, Ivens S, Bechmann I, Tomkins O, Heinemann U, et al. Lasting blood-brain barrier disruption induces epileptic focus in the rat somatosensory cortex. J Neurosci 2004;24:7829-36.

19. Uva L, Librizzi L, Marchi N, Noe F, Bongianni R, Vezzani A, et al. Acute induction of epileptiform discharges by pilocarpine in the in vitro isolated guinea-pig brain requires enhancement of blood-brain barrier permeability. Neuroscience 2008;151:303-12.

20. van Vliet EA, Aronica E, Gorter JA. Blood-brain barrier dysfunction, seizures and epilepsy. Semin Cell Dev Biol 2015;38:26-34.

21. Tomkins O, Feintuch A, Benifla M, Cohen A, Friedman A, Shelef I. Blood-brain barrier breakdown following traumatic brain injury: A possible role in posttraumatic epilepsy. Cardiovasc Psychiatry Neurol 2011;2011:765923.

22. Mantovani A, Garlanda C, Doni A, Bottazzi B. Pentraxins in innate immunity: From C-reactive protein to the long pentraxin PTX3. J Clin Immunol 2008;28:1-13.

23. Alapitti T, Waris M, Faila M, Soili-Hänninen M, Mäkinen R, Kharazmi E, et al. C-reactive protein and seizures in focal epilepsy: A video-electroencephalographic study. Epilepsia 2012;53:790-6.

24. Tan TY, Lu CH, Chuang HY, Lin TK, Liou CW, Chang WN, et al. Long-term antiepileptic drug therapy contributes to the acceleration of atherosclerosis. Epilepsia 2009;50:1579-86.