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Evaluation of Serum Interleukin-1β (IL-1β) Levels in Patients with Intracranial Aneurysms Compared to a Control Group

Abdolkarim RAHMANIAN[1], Nasser GHOLIJANI[2], Mohammad SALEHI[1], Arash SAFFARIAN[1], Mohammad JAMALI[1], Keyvan EGHBAL[1], Ehsan Mohammad HOSSEINI[1], Abbas RAKHSHA[1]

[1]Shiraz University of Medical Sciences, Department of Neurosurgery, Shiraz, Islamic Republic of Iran
[2]Shiraz University of Medical Sciences, Department of Immunology, Shiraz, Islamic Republic of Iran

Corresponding author: Ehsan Mohammad HOSSEINI ✉ Ehsan_m_h76@yahoo.com

ABSTRACT

AIM: Intracranial aneurysm (ICA) is a relatively common disease with a fairly high prevalence in the general population. Multiple inflammatory factors, which play a significant role in the formation of cerebral aneurysms, have been investigated.

This study aimed to examine the screening value of the serum level of interleukin-1β (IL-1β) in aneurysmal subarachnoid hemorrhage (SAH) and to evaluate its association with the severity of initial bleeding.

MATERIAL and METHODS: This case-control study was performed in Namazi Hospital, affiliated to Shiraz University of Medical Sciences, Shiraz, Iran. The study population included patients referred to Namazi Hospital with a diagnosis of SAH, whose symptoms had emerged within less than 48 hours. The case group consisted of patients with cerebral aneurysms, who were divided into two groups of raptured and un-raptured brain aneurysms. This study examined the relationship between the serum IL-1β levels and brain aneurysms. The number of samples was 43 per group and 86 in total. Forty-eight hours before the onset of symptoms and before surgery, a blood sample was collected to measure the IL-1β antibody (anti-IL-1β) level; in less than three hours, the serum was isolated and placed in a -80°C freezer.

RESULTS: In patients with unruptured aneurysms, the Fisher's grade was 0, while most ruptured aneurysms were grade 3. The middle cerebral artery (MCA) (n=10, 23%) was the most common site of aneurysm, followed by the anterior communicating artery (ACom) (n=9, 20%). There was a significant correlation between ruptured aneurysms and the Glasgow Comma Scale (GCS) score (p=0.01) and also Fisher's classification (p=0.04). Patients with ruptured and unruptured aneurysms showed no significant differences regarding the serum IL-1β levels. A significant difference was found in the serum level of IL-1β between the case and control groups (p=0.04).

CONCLUSION: Generally, knowledge of the association between aneurysm development and inflammatory response can have significant clinical implications in the future. The present findings suggested a significant correlation between the IL-1β levels and the outcomes of aneurysmal SAH, independent of initial hemorrhage.

KEYWORDS: Neuroinflammation, Aneurysmal subarachnoid hemorrhage, IL-1β

INTRODUCTION

Intracranial aneurysm (ICA) is a common disease in the general population, with an estimated prevalence of 5-8% (2). Although ICA frequently remains undiagnosed due to the absence of symptoms, it may cause significant intracranial hemorrhage (2). On the other hand, there are several reports of ICAs with no rupture in the life-long follow-ups. Today, only invasive procedures (i.e., microsurgical or endovascular occlusion), which are associated with the risk of morbidity and even mortality, are used to prevent ICA

Abdolkarim RAHMANIAN : 0000-0001-5223-7083
Nasser GHOLIJANI : 0000-0002-8040-3189
Mohammad SALEHI : 0000-0003-4557-7287
Arash SAFFARIAN : 0000-0002-2935-5927
Mohammad JAMALI : 0000-0002-1985-3850
Keyvan EGHBAL : 0000-0001-6185-8367
Ehsan Mohammad HOSSEINI : 0000-0002-0065-0420
Abbas RAKHSHA : 0000-0001-9561-9874

rupture (3). The aneurysm location has been introduced as a potential predictor of aneurysm rupture (17). Most cases of subarachnoid hemorrhage (SAH) are caused by the rupture of small aneurysms. However, it remains unclear which small unruptured ICAs are at risk of rupture, and preventive approaches seem necessary (5).

Multiple inflammatory factors have been reported to play a substantial role in cerebral aneurysm formation (4). Evidence suggests that proinflammatory interleukins (ILs) can start a cascade of biochemical alterations in ischemic brain injury (3). Vasospasm associated with SAH is the cause of ischemic changes in the brain. The immunological mechanism can cause degenerative/generative alterations in the walls of vessels in delayed vasospasm following SAH, resulting in significant vasospasm responsible for cerebral ischemia (8). Moreover, emerging findings show that proinflammatory cytokines may be involved in the pathogenesis of ICAs (17,20).

Interleukin-1β (IL-1β) is a proinflammatory cytokine, which plays an essential role in both acute and chronic central nervous system damages. Delayed cerebral ischemia is one of the main causes of morbidity following aneurysmal SAH (19). The majority of unruptured aneurysms that are identified by accident have a stable clinical course, which indicates a lower rate of inflammatory or degenerative alterations in the vessel walls, besides a low rupture risk. Nonetheless, some unruptured aneurysms show important alterations in shape and size with a higher risk of rupture. These aneurysms can rupture in the initial stage of development or become larger in a short period, considering the thinning of vessel walls due to degenerative alterations (13).

Inflammatory cells, such as T lymphocytes, macrophages, and monocytes, can be detected in the aneurysm walls. Leukocyte infiltration occurs due to the elimination or impairment of collagen fibers. It is known that the plasma concentrations of collagenases, cytokines, and elastases increase in patients with cerebral aneurysms (11,15,18). The present study aimed to measure the serum level of IL-1β and to examine its potential as a prognostic inflammatory factor in ICAs. Two groups of patients with ruptured and unruptured aneurysms were compared with the healthy controls.

Galea J. et al. administered 100 mg of subcutaneous interleukin-1 receptor antagonist (IL-1Ra) twice daily in patients with aneurysmal SAH. They found that IL-1Ra significantly decreased the levels of IL-6 and C-reactive protein (CRP). Besides, fibrinogen levels decreased in the active arm of the study. Overall, subcutaneous IL-1Ra was safe and well-tolerated by SAH patients; it was also effective in decreasing peripheral inflammation (9). Moreover, Wu W. et al. assessed the relationship between SAH progression and tumor necrosis factor-alpha (TNF-α) and IL-6 concentrations in the cerebrospinal fluid (CSF). They found increased IL-6 and TNF-α concentrations in the CSF of patients with cerebral vasospasm (CVS) compared to non-CVS patients. Moreover, the IL-6 and TNF-α concentrations in the CSF were significantly higher in SAH cases compared to the healthy controls. However, robust evidence is needed to confirm if IL-6 and TNF-α levels in the CSF increase in SAH and contribute to its development (21). Additionally, Yue Y. et al. reported that changes in leukocytes in the serum and changes in IL-1β in the CSF affected the neurological consequences of traumatic brain injury. They found that with an increase in the Glasgow Outcome Score (GOS), the level of IL-1β decreased, while with a decrease in the GOS score, the IL-1β level increased (22).

MATERIAL and METHODS

Study Design

This case-control study was performed in Namazi Hospital, affiliated to Shiraz University of Medical Sciences, Shiraz, Iran, in 2016. The study population included patients referred to Namazi Hospital with a diagnosis of SAH, whose symptoms had emerged within less than 48 hours. The case group consisted of patients with cerebral aneurysms, who were divided into two groups of raptured and unraptured brain aneurysms.

After statistical consultation, considering the absence of similar human studies on the relationship between serum IL-1β levels and brain aneurysms, this research was conducted as a preliminary study by providing anti-IL-1β antibody kits. The number of samples was 43 in each group and 86 in total. For all of the participants, at 48 hours before the onset of symptoms and before surgery, a blood sample was taken to measure the anti-IL-1β antibody level; in less than three hours, the serum was isolated and placed in a -80°C freezer. Moreover, samples were collected from patients with unruptured aneurysms, who were either undergoing surgery or being monitored.

The control group was selected from the blood bank samples of the immunology department. The subjects in the control group were similar to the case group in terms of age and sex. They had no history of rheumatic disease, inflammatory diseases, or cancer. They also had no symptoms of headache or dizziness, no history of cerebral aneurysm, and no history of cerebral aneurysm in their first-degree relatives.

Statistical Analysis

Descriptive data were analyzed in SPSS Version 23.0. Tables and figures were drawn, and *t*-test, Fisher's exact test, and Mann-Whitney test were performed for data analysis. Descriptive statistics were measured to represent the data. Data are expressed as mean standard deviation (SD) or frequency and percentage (%). A P-value less than 0.05 was considered statistically significant.

Data Collection

To conduct this study, the Neurosurgery Department of Namazi Hospital affiliated to Shiraz University of Medical Sciences allowed access to cases. The data collection tools included data collection forms, which were designed based on the Neurosurgery Department protocols. These forms were completed by the researcher after examining the cases.

Inclusion Criteria

The inclusion criteria were as follows: 1) Patients investigated in the Neurosurgery Department of Namazi Hospital; 2) patients

Table I: Frequency Distribution of Variables, Including Age and Sex, in Ruptured and Unruptured Case Groups and the Control Group

Variable		Subgroup		Control group (n=43)	p
		Rupture (n=32)	Unruptured (n=11)		
Age * (Mean ± SD)		49.00 ± 10.01	49.47 ± 13.27	49.21 ± 11.08	0.9
Sex**	Male	16 (76.2%)	5 (23.8%)	19 (44.1%)	0.08
	Female	16 (72.7%)	6 (27.3%)	24 (55.8%)	0.07

**T-test for evaluation of age distribution.*
***Mann-Whitney U test for evaluation of sex distribution.*

Table II: Frequency Distribution of Variables in the Ruptured and Unruptured Groups

Variable	Subgroup		p
	Rupture	Unruptured	
Aneurysm size*	8.59 ± 4.37	11.73 ± 8.7	0.06
Fisher * classification	2.91 ± 0.73	0	0.04
H & H scale*	2.53 ± 0.95	1	0.07
GCS score*	12.97 ± 2.93	15	0.01

**T-test with mean±SD.*

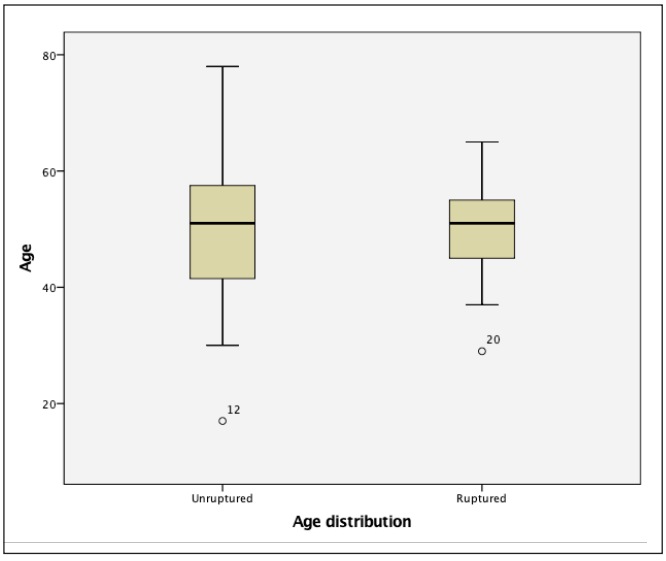

Figure 1: Frequency distribution of the patients' age with regard to ruptured and unruptured aneurysms.

diagnosed with aneurysms on CT scan; and 3) patients with complete information and follow-up data.

Exclusion Criteria

The exclusion criteria were as follows: 1) Incomplete cases; 2) patient's unwillingness to continue the study; 3) patients with a history of cancer; and 4) patients with a history of inflammatory or autoimmune disorders due to interactions with IL-1β.

Ethical Considerations

The participants were ensured about the confidentiality of their information. This study was performed according to the Declaration of Helsinki guidelines. The study protocol was also approved by the Ethics Committee of Shiraz University of Medical Sciences, research project number IR.SUMS.MED.REC.1398.013, the experiments were performed in the neurosurgery department of this university.

RESULTS

Based on the findings, the mean age difference of patients in the ruptured and unruptured group was not statistically significant. The frequency distribution of the patients' age were shown in Figure 1.

21 patients were male and 22 were female but the difference was not statistically significant. The frequency distribution of variables, including age and sex, in ruptured and unruptured cases and the control groups are shown in Table I.

The Fisher's average grade was 0 in patients with unruptured aneurysms, while it was 2.91 in patients with ruptured aneurysms. The Fisher's grade and Hunt & Hess (H&H) scale scores of the case group are presented in Table II. The serum level of IL-1β was significantly lower in patients with aneurysms compared to the healthy subjects (p=0.04). On the other hand, a significant difference was found in the serum IL-1β levels between patients with ruptured and unruptured aneurysms.

The aneurysms location was also investigated in this study. The most common site of aneurysm was MCA (n=10, 23%), followed by the anterior communicating artery (ACom) (n=9,

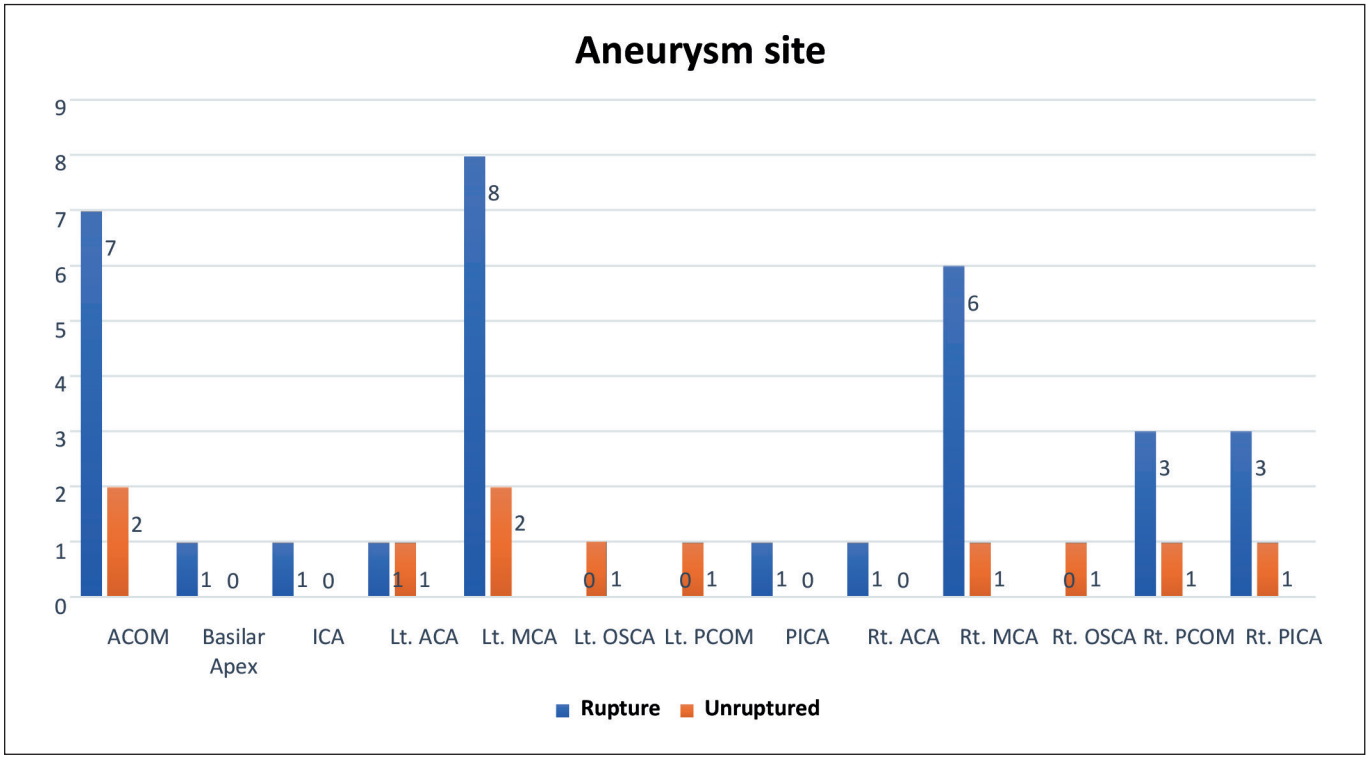

Figure 2: Frequency distribution of the aneurysm site in patients with ruptured and unruptured aneurysms (p=0.54)

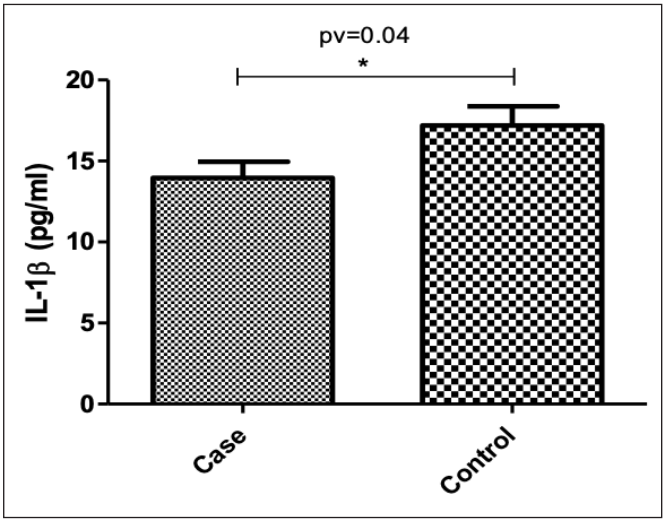

Figure 3: Frequency distribution of serum IL-1β levels in the case and control groups

20%). The distribution of aneurysms is shown in Figure 2 and Table III.

There was a significant correlation between the GCS scores and ruptured or unruptured aneurysms (p=0.01) and Fisher's classification (p=0.04). However, no significant difference was found in the maximal aneurysm size (p=0.6). No significant difference was also found regarding the sex and age of patients with ruptured and unruptured aneurysms (p=0.8 and p=0.9, respectively).

According to the results, there was no significant difference between the serum levels of IL-1β in patients with ruptured and un-ruptured aneurysms. But there was a significant difference between the serum levels of IL-1β in cases and controls (p=0.04).

The frequency distribution of serum IL-1β levels in the case and control groups is presented in Figure 3.

DISCUSSION

ICAs classically develop after the second decade of life or between the fourth and sixth decades of life and are predominant in women. Around 25% of patients with unruptured aneurysms have more than one aneurysm. The rupture of an ICA results in SAH (6,7). The prognosis of SAH is poor in several cases despite improvements in endovascular and microsurgical management (1). The vascular endothelial cell secretes extracellular matrix proteins, which help maintain the structural integrity of aneurysm in the aneurysm wall against the internal pressure of aneurysm (12). Inflammatory reactions are among key mechanisms that result in ischemic damage to the brain following SAH (10). Abnormal vascular transformation, facilitated by inflammatory cells, is recognized as the pathological component of various vascular diseases, including aneurysms, arteriovenous malformations, and atherosclerosis (11). Besides, neuroinflammation plays a major role in brain injury.

The intracranial vasculature is exposed to endothelial cell dysfunction, and red blood cell breakdown can lead to the release of inflammatory cytokines, resulting in vasospasm and tissue damage (16). These processes cause dilation, remodeling,

Table III: Frequency Distribution of Aneurysm Site in Patients With Ruptured and Unruptured Aneurysms (p=0.54)

Aneurysm site*	Subgroups		Total
	Ruptured	Unruptured	
ACom	7	2	9
Basilar apex	1	0	1
ICA	1	0	1
Lt. ACA	1	1	2
Lt. MCA	8	2	10
Lt. SCA	0	1	1
Lt. PCom	0	1	1
Lt. PICA	1	0	1
Rt. ACA	1	0	1
Rt. MCA	6	1	7
Rt. SCA	0	1	1
Rt. PCom	3	1	4
Rt. PICA	3	1	4
Total	32	11	43

**Fisher's exact test.*
ACA: *Anterior cerebral artery;* ***MCA:*** *Middle cerebral artery;* ***PCom:*** *Posterior communicating artery;* ***PICA:*** *Posterior inferior cerebellar artery;* ***SCA:*** *Superior cerebellar artery.*

and weakening of vessel walls as important components of aneurysm formation and rupture (1). In atherosclerotic lesions, inflammatory cells, such as leukocytes and macrophages, affect the vascular pathology. Many proteases are secreted by these cells to destroy proteins in the extracellular matrix. Macrophages are the main inflammatory cells in atherosclerosis, and leukocytes cause acute inflammation. Evidence shows that wall invasion occurs by macrophages and leukocytes in ruptured aneurysms, and leukocytes in the wall can be related to SAH (14).

The assessment of changes in the concentrations of IL-6 and IL-1β in the CSF of patients following SAH, as well as confirmation of their effects on ischemic brain damage and delayed vasospasm, seems important for understanding the mechanisms (20). Inflammatory cascades seem to be involved in vascular smooth muscle cell (VSMC) dysfunction and death. Overall, IL-1β, as a proinflammatory cytokine, has harmful effects on the extracellular matrix and VSMCs. It also directly stimulates the apoptosis of VSMCs, leading to the thinning of aneurysm wall. According to a previous study, the effect of IL-1β on VSMC degradation can result in aneurysm development in IL-1β-deficient mice (1).

Our increased understanding of the association between inflammatory reactions and aneurysm development can have significant clinical implications in the future (1). In Iran, there are no extensive studies on the association of SAH with proinflammatory cytokines. We found that the serum level of IL-1β was significantly lower in patients with aneurysms compared to healthy individuals. Also, no significant difference was found in the serum IL-1β levels between patients with ruptured and unruptured aneurysms.

CONCLUSION

Overall, knowledge of the association between inflammatory reactions and aneurysm development can have significant clinical implications in the future. The present findings indicated no significant correlation between the IL-1β levels and the outcomes of aneurysmal SAH, regardless of the initial hemorrhage.

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AUTHORSHIP CONTRIBUTION

Study conception and design: AKR, MJ, EMH, AS, KE

Data collection: NG, MS

Analysis and interpretation of results: AKR, AS, KE, AR, NG, MJ

Draft manuscript preparation: EMH, MS

Critical revision of the article: AR, NG, MS, AS, MJ, KE, EMH, AR

Other (study supervision, fundings, materials, etc...): AKR, EMH

All authors (AR, NG, MS, AS, MJ, KE, EMH, AR) reviewed the results and approved the final version of the manuscript.

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