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Subfatin, asprosin, alamandine and maresin-1 in cerebral ischemia, intracranial and subarachnoid hemorrhages

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Abstract. – OBJECTIVE: Cerebrovascular diseases (CVDs) remain an important public health issue due to the increasing number of deaths worldwide. Changes in the synthesis and release of peptides in CVDs may play an important role in elucidating the physiopathology of the disease. Therefore, this study was to investigate the fate of maresin-1 (MaR-1), subfatin (SUB), asprosin (ASP), and alamandine (ALA) levels in patients with cerebral infarction (CI), intracranial hemorrhage (ICH), subarachnoid hemorrhage (SAH) evaluated within the scope of CVDs, and voluntary healthy controls.

PATIENTS AND METHODS: The study participants were divided into 4 groups: CI patients, ICH patients, SAH patients, and healthy volunteers. The diagnosis of CVDs was made based on the National Institutes of Health Stroke Scale (NIHSS), Intracerebral Hemorrhage Score (ICHS), Botterel-Hunt-Hess Scale (BHHS), and cranial computed tomography (CT). The levels of MaR-1 (ng/mL), SUB (ng/mL), ASP (ng/mL), and ALA (pg/mL) in the blood samples collected from the participants were studied using the ELISA method. Other parameters included in the study were obtained from the patient records of our hospital.

RESULTS: The comparison of MaR-1 [(control 1.38 ± 0.14), SAH (0.98 ± 0.087), CI (0.67 ± 0.04), ICH (0.51 ± 0.03)], SUB [(control (13.2 ± 1.4), SAH (10.1 ± 1.2), CI (7.9 ± 0.8), ICH (5.8 ± 0.5)], and ALA [(control (67.2 ± 7.9), SAH (58.2 ± 4.3), CI (42.1 ± 3.7), and ICH (34.2 ±3.9)] values revealed a significant decrease compared to the control values. The comparison of the ASP values of SAH, CI, and ICH patients and control values (11.6 ± 1.2) showed significantly higher asprosin values in SAH (13.8 ± 1.1), CI (15.4 ± 1.2) and ICH (28.9 ± 2.8) patients. Similarly, systolic blood pressure (SBP), diastolic blood pressure (DBP), and glucose levels of CKD patients were also high.

CONCLUSIONS: Decreased MaR-1, SUB, ALA and increased ASP compared to the control values may play a role in the physiopathology of these diseases. MaR-1, SUB, ALA, and ASP differences between SAH, CI and ICH patients may also guide clinicians along with SBP, DBP and glucose values.

Key Words:
Maresin-1, Subfatin, Asprosin, Alamandine, Cerebral ischemia, Hemorrhagy.

Introduction

Cerebrovascular diseases (CVDs) (includes all disorders in which an area of the brain is temporarily or permanently affected by ischemia or bleeding) are second important cause of death after coronary vascular diseases in developed countries[1]. Moreover, the quality of life of survived patients is very poor[2]. The incidence of cerebral ischemia (CI), intracranial hemorrhage

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(ICH), and subarachnoid hemorrhage (SAH) is 80%, 15%, and 5%, respectively, in CVDs which also affect organs other than the brain[3-6]. In such a case, one of the most affected organs is the endocrine tissues. Because adipose endocrine tissues might have the capacity to regulate the bioactive peptides or anti-inflammatory molecules they produce locally to compensate for the negative change in patients with CI and ICH or SAH[7,8].

Numerous inflammatory mediators such as macrophages, neutrophils, monocytes, cytokines, chemokines, leukocytes, and adhesion molecules have been shown in and around ischemic tissue after CI, ICH, and SAH[9,10]. Therefore, inflammation has a role in the pathogenesis of stroke, ICH, and SAH. Maresin-1 (MaR-1), which has been discovered in recent years, is a pro-resolving lipid mediator synthesized [this biosynthesis includes an active intermediate (13S,14S-epoxy-DHA) that stimulates the conversion of macrophage from M1 (anti-inflammatory) to M2 (anti-inflammatory) phenotype] by macrophages that regulates acute inflammation, has anti-inflammatory properties, and promotes tissue regeneration[11,12]. MaR-1 has been reported[13] to have the potential to treat postoperative neuroinflammation, neurocognitive dysfunction, and is a molecule that accelerates surgical wound healing in planarians and provides organ regeneration and tissue healing[14,15]. Plasma MaR-1 concentrations are associated with diabetic foot ulcer, obesity, glucose and lipid metabolism disorders, and insulin secretion and resistance[16,17]. Due to all these properties, it is beneficial to investigate the fate of MaR-1 after CI, ICH, and SAH.

In addition, the decrease in blood supply to the brain in CI, ICH, and SAH results in energy deficiency[18]. Thus, changes occur in glucose metabolism. The major source of energy for the brain is glucose[19]. About 100 g of brain tissue consumes 30 mmol (5 mg) of glucose in 1 minute. This corresponds to approximately 125 gr/day glucose. Glucose enters the brain by facilitated transport[20]. About 80% of it is used to produce energy, while the remaining is used in the synthesis of neurotransmitters, proteins and lipids. As end product, it is metabolized to lactate[19]. In CI, ICH, and SAH, the level of energy metabolites such as ATP and phosphocreatine decreases, while lactate levels increase[21,22]. All these events result in metabolic imbalance. Subfatin (SUB) and asprosin (ASP), which have been discovered in recent years, are two important metabolic molecules that are synthesized mainly in the adipose tissue[23]. Small amounts of these two molecules have been reported to be synthesized in other tissues, including salivary glands[24-26]. Furthermore, these two molecules play a role in inflammation, insulin resistance, and regulation of glucose metabolism[27-28]. In other words, SUB and ASP are the new important players of metabolic events[27-29]. A study reported that a decrease in SUB and ASP levels may cause a decrease in metabolic activity, preventing adequate energy production and thereby increasing oxidative stress in patients30,31. As mentioned above, since many metabolic pathways, including glucose metabolism, are affected in patients with CI, ICH, and SAH, it is useful to investigate the status of SUB and ASP, which keep glucose metabolism under strict control.

Approximately 80% of patients with ischemic stroke have hypertension[32,33]. Alamandine (ALA) is a new hormone in the heptapeptide (Ala-Arg-Val-Tyr-Ile-His-Pro) structure of the renin-angiotensin system (RAS) that regulates blood pressure[34,35]. ALA also reduces aortic constriction, improves cardiovascular functions, and regulates cardiac contractility, growth, and apoptosis[36]. In addition, ALA is a hormone with vasodilatory, antifibrotic, anti-inflammatory[37], and antihypertensive effects[35]. ALA exerts its biological effects using its receptor Mas-related G protein-coupled receptor D (MrgD)[38]. The presence of the MrgD has been demonstrated in cell membrane, cytoplasm, perinuclear and nuclear regions of brain cells, cardiomyocytes, aorta, endothelial cells, and retina[38-41]. ALA is a product of ACE2-dependent catalytic hydrolysis of angiotensin A (Ang A). It can also be derived directly from Ang (1-7) by decarboxylation of the N-terminal aspartic acid residue[34]. Based on the above-mentioned data, there may be a relationship with ALA in patients with CI, ICH, and SAH.

Although computed tomography (CT) and magnetic resonance imaging (MRI) already have high sensitivity and specificity for the diagnosis of ischemia, their limited use, technical difficulties and cost make CT and MRI-based studies less practical in the acute setting[42]. Therefore, there is a need for new diagnostic analytical biomarkers to establish a rapid and accurate diagnosis of ischemic stroke. According to the results of the extensive literature review, the fate of MaR-1, SUB, ASP, and ALA in patients with CI, ICH, and SAH has not yet been investigated. Considering all the above-mentioned information, the primary aim of this study is to investigate MaR-1, SUB, ASP, and ALA levels in patients with CI, ICH, SAH, and healthy controls and to reveal whether they have a role in the diagnosis of these diseases.

Patients and Methods

This study was conducted after obtaining the approval of the Clinical Research and Ethics Committee (issue 9/41/dated 6/7/ 2022) and written informed consent from patients. The study included a total of 4 groups: 22 patients with CI, 22 patients with ICH, and 22 patients with SAH who presented and were admitted to the Neurosurgery Clinic of Fethi Sekin City Hospital, and 26 healthy controls. The National Institutes of Health Stroke Scale (NIHSS), Intracerebral Hemorrhage Score (ICHS), and Botterel-Hunt-Hess Scale (BHHS) were used for CI, ICH and SAH patients, respectively[43-46] and the diagnosis of CI, ICH, and SAH was confirmed by early cranial computed tomography (CT) (Figure 1). The control group consisted of healthy volunteers who presented to our hospital for a routine check-up.

Patients with previously known chronic obstructive pulmonary disease (COPD) and liver disease, acute myocardial infarction (MI), diabetes mellitus, kidney failure, a history of hypothyroidism and hyperthyroidism, cardiac cachexia, morbidly obese patients, patients under the age of 18 and over the age of 80, patients with an active infection and a history of previous cerebrovascular disease were excluded from the study. Body mass index (BMI) of the participants was calculated by dividing the weight in kilograms by height in meters. Five mL of venous blood were collected between 09-17.00 hours from the patients and control groups into biochemistry tubes containing aprotinin (500 KIU: Kallikrein Inhibitor Unit)[47]. These blood samples were centrifuged at 4,000 rpm for 5 minutes. The obtained plasma was divided into 5 equal parts and stored at -40°C in Eppendorf tubes until analysis. Glucose values of the patient and control groups were obtained from the hospital records.

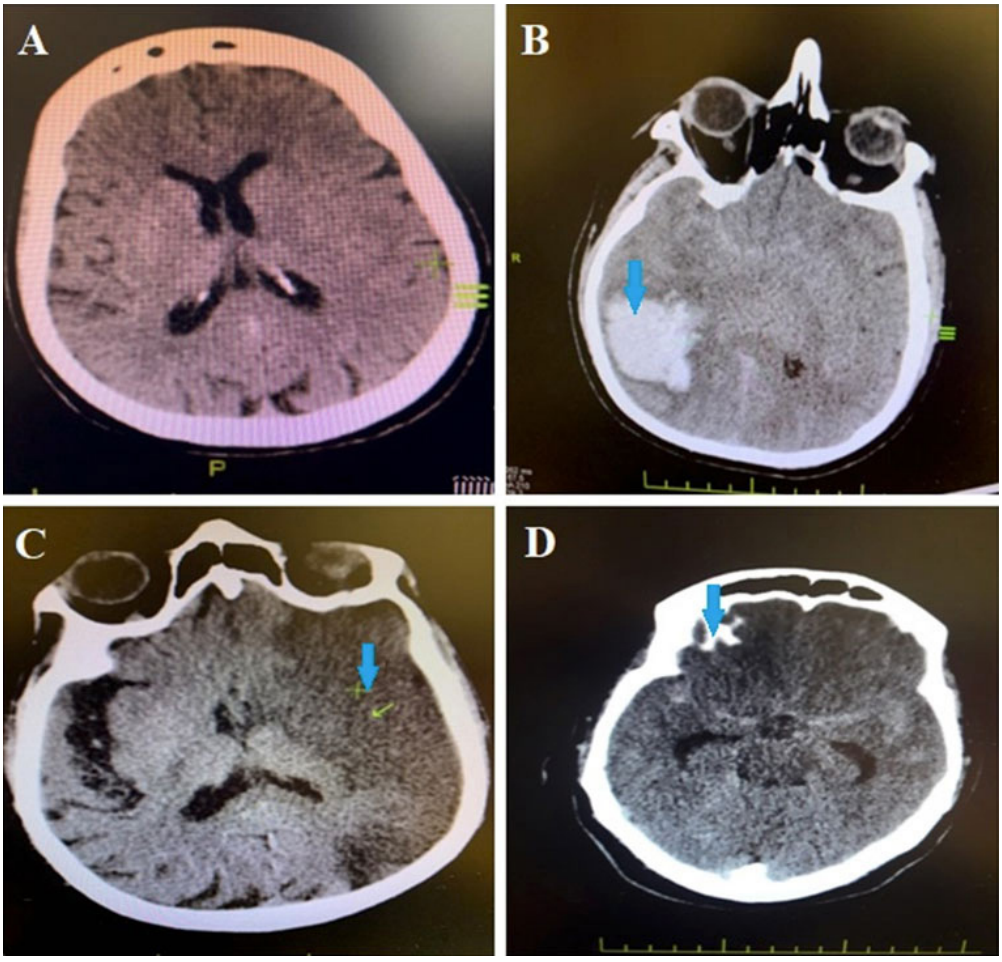

Figure 1. Comparison of cranial computed tomography (CT) of Control (**A**), SAH (**B**), CI (**C**), and ICH (**D**) patients. SAH: Subarachnoid haemorrhage; CI: Cerebral infarction; ICH: Intracranial haemorrhage. Arrows indicate pathological areas.

Measurements of Biochemical Molecules by ELISA

The ELISA method was used to determine the levels of (Meteorin-like protein) SUB (Bioassay Technology Laboratory; catalog No.: E3941Hu, Yangpu Dist, Shanghai, China), ASP (Bioassay Technology Laboratory; catalog No.: E4095Hu Yangpu Dist, Shanghai, China), ALA (SunRed, Biological Technology Co.; catalog No.: DZE201125722 Baoshan District, Shanghai, China), MaR-1 (SunRed, Biological Technology Co.; catalog No.: DZE201127349, Baoshan District, Shanghai, China) in accordance with the manufacturer's kit procedures. Absorbances were read spectrophotometrically at 450 nm on a ChroMate Microplate Reader P4300 (Awareness Technology Instruments, Westport, CT, USA). Bio-TEK ELX50 (BioTek Instruments, Winooski, VT, USA) was used as an automated washer for washing plates. The measurable range of the kit for SUB was 0.05-15 ng/ml with a minimum of 0.01 ng/mL. The measurable range of the kit for ASP was 0.5-100 ng/mL, with a minimum of 0.23 ng/mL. The measurable range of the kit for ALA was 1.5-400 pg/mL, with a minimum of 1.368 pg/ml. The measurable range of the kit for MaR-1 kit was 0.01-1.5 ng/mL. The intra-assay and inter-assay CV values of the kits were < 10% and < 15%, respectively.

Statistical Analysis

All statistical analyses were performed using a software package SSPS, version 22 (IBM Corp., Armonk, NY, USA). In addition to descriptive statistical methods [Standard deviation (SD)], multifactorial regression analysis test was used for comparisons when analyzing the study data. The results were evaluated at a 95% confidence interval. The level of significance was accepted as $p < 0.05$.

Results

The demographic characteristics of the patients and healthy controls are shown in Table I. The comparison of the SBP (mm Hg) and DBP (mm Hg) values of the participants revealed a significant increase in these values, gradually rising from controls toward SAH, CI, and ICH patients (Table I; $p < 0.05$). The blood glucose values measured after SAH, CI, and ICH were higher compared to control values (Table I; $p < 0.05$). There was no significant difference in other parameters evaluated (Table I). Figure 1 shows the CT evaluation of the participants.

The MaR-1 levels of SAH, CI, and ICH patients were significantly lower compared to healthy controls ($p < 0.01$). In other words, the MaR-1 values were 1.38 ± 0.14 ng/mL in healthy controls, 0.98 ± 0.087 ng/mL in SAH patients, 0.67 ± 0.04 ng/mL in CI patients, and 0.5 ± 0.03 ng/m in ICH patients (Figure 2).

Similarly, the SUB levels of SAH, CI, and ICH patients were significantly lower compared to healthy participants ($p < 0.01$). In other words, the SUB values were 13.2 ± 1.4 ng/mL in healthy controls, 10.1 ± 1.2 ng/mL in SAH patients, 7.9 ± 0.8 ng/mL in CI patients, and 5.8 ± 0.5 ng/m in ICH patients (Figure 3).

The ALA levels of SAH, CI, and ICH patients were significantly lower compared to healthy controls ($p < 0.05$). Particurlarly, the ALA values were 67.2 ± 7.9 ng/mL in healthy controls, 58.2 ± 4.3ng/mL in SAH patients, 42.1 ± 3.7 ng/mL in CI patients, and 34.2 ± 3.9 ng/mL in ICH patients (Figure 4).

However, the ASP levels of SAH, CI and ICH patients were significantly higher compared to healthy controls ($p < 0.05$). In other words, the ASP values were 11.6 ± 1.2 ng/mL in healthy controls, 13.8 ± 1.1 in SAH patients, 15.4 ± 1.2 ng/mL in CI patients, and 28.9 ± 2.8 ng/mL in ICH patients (Figure 5).

Table I. Comparison of demographic characteristics and glucose values of patients with control values.

Parameters	Control	SAH	CI	ICH
BMI (kg/m²)	28.4 ± 2.7	32.1 ± 3.6	31.2 ± 2.9	29.8 ± 4.1
Sex (F/M)	12/14	11/11	9/13	10/12
Age (year)	68.8 ± 3.1	62.7 ± 2.9	69.2 ± 2.9	67.6 ± 5.2
SBP (mm Hg)	124.2 ± 9.82	139.8[a] ± 11.94	156.82[a] ± 19.3	162.21[a] ± 27.12
DBP (mm Hg)	82.1 ± 7.42	87.2 ± 8.53	86.9 ± 7.42	89.4 ± 6.92
Glucose (mg/dL)	94.72 ± 8.56	122.8[a] ± 11.2	144.62[a,b] ± 12.8	168.44[a,b] ± 23.1

Control *vs.* SAH[a], CI[a], ICH[a] ($p = 0.02$). SAH *vs.* CI[b], ICH[b] ($p = 0.05$).

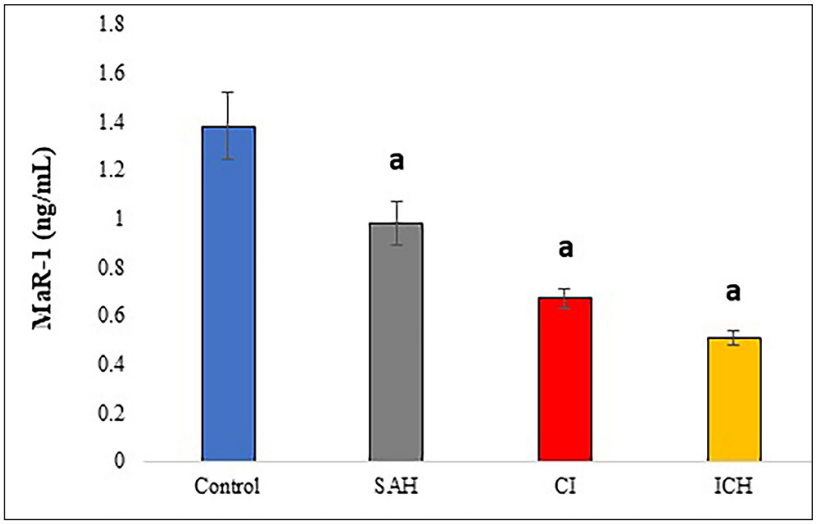

Figure 2. Comparison of MaR-1 values of SAH, CI and ICH patients with the control group. SAH: Subarachnoid haemorrhage; CI: Cerebral infarction; ICH: Intracranial haemorrhage. a = *vs.* control group ($p < 0.05$).

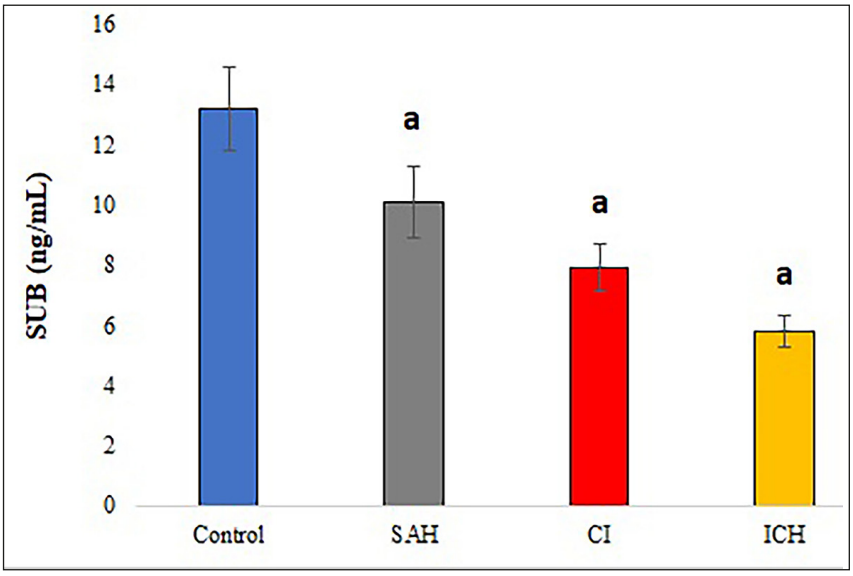

Figure 3. Comparison of SUB values of SAH, CI and ICH patients with the control group. a = *vs.* control group ($p < 0.05$).

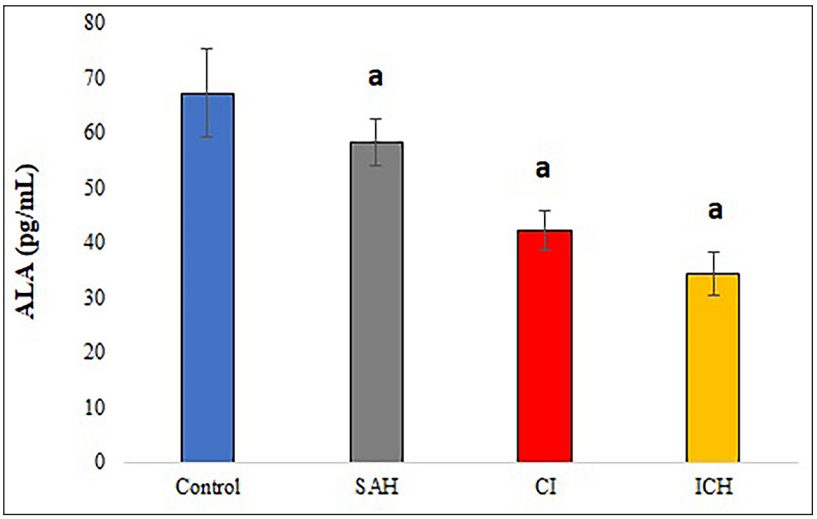

Figure 4. Comparison of ALA values of SAH, CI and ICH patients with the control group. SAH: Subarachnoid haemorrhage; CI: Cerebral infarction; ICH: Intracranial haemorrhage. a = *vs.* control group ($p < 0.05$).

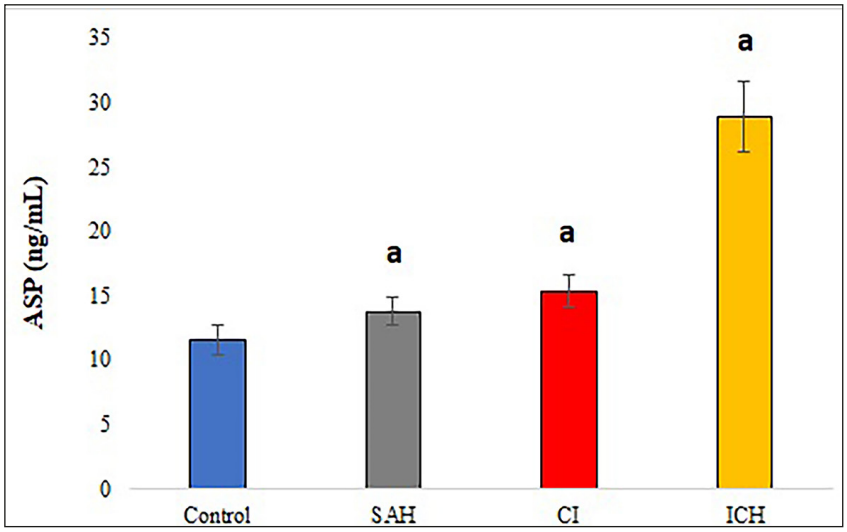

Figure 5. Comparison of ASP values of SAH, CI and ICH patients with the control group. SAH: Subarachnoid haemorrhage; CI: Cerebral infarction; ICH: Intracranial haemorrhage. a = *vs.* control group ($p < 0.05$).

There was a positive correlation between the glucose and SBP values of SAH (r: 0.57, $p < 0.02$), CI (r: 0.61, $p < 0.01$), and ICH (r: 0.42, $p < 0.05$), patients. Similarly, a positive correlation was noted between the glucose and SBP values of SAH (r: 0.56, $p < 0.01$), CI (r: 0.46, $p < 0.03$), and ICH (r: 0.49, $p < 0.05$), patients. There was a negative correlation between the MaR-1 and ASP values of SAH (r: -0.48, $p < 0.01$), CI (r: -0.44, $p < 0.05$), and ICH patients (r: -0.52, $p < 0.02$). There was a negative correlation between the SUB and ASP values of SAH (r: -0.62, $p < 0.01$), CI (r: -0.48, $p < 0.03$), and ICH (r: -0.54, $p < 0.01$), patients. A negative correlation was found between the ALA and ASP values of SAH (r: -0.56, $p < 0.01$), CI (r: -0.44, $p < 0.05$), and ICH patients (r: -0.47, $p < 0.02$). There was a correlation between the glucose and ASP values of SAH (r: 0.47, $p < 0.05$), CI (r: 0.43, $p < 0.05$), and ICH (r: 0.48, $p < 0.05$) patients.

Discussion

Stroke is the second leading cause of death worldwide[1]. The adjusted prevalence of stroke is around 6.94/1,000 inhabitants[48]. Stroke is an important health issue that negatively affects the health and economy of both individuals and countries[3]. The underlying physiopathology of the disease has not yet been fully elucidated. Therefore, this study investigated the roles of MaR-1, SUB, ASP and ALA molecules in patients with CI, ICH, and SAH.

In this study, the MaR-1 levels of SAH, CI and ICH patients were significantly lower compared to healthy controls. Occlusion or narrowing of cerebral vessels increases inflammation[49]. The possible reason for the low MaR-1 values in SAH, CI and ICH patients may have led to an increase in the inflammation caused by these diseases and a decrease in the circulating levels of MaR-1, a strong endogenous anti-inflammatory molecule[14], consumed by the organism to eliminate this inflammation. The administration of MaR-1 decreases inflammation[50]. MaR-1 levels have been reported to decrease in diseases characterized by inflammation such as diabetes[51], and polycystic ovary syndrome (PCOS)[52]. Another study[53] reported that Mar-1 also alleviated renal ischemia/reperfusion injury in mice *via* inhibition of the TLR4/MAPK/NF-κB pathways and activation of the Nrf2 pathway. Another study[54] found that MaR-1 protected the liver against hepatic I/R injury *via* an ALXR/Akt signaling pathway. According to these data, we anticipate that it may have decreased due to the use of circulating MaR-1 in SAH, CI and ICH patients to eliminate inflammation.

Moreover, in this study, the SUB levels of SAH, CI and ICH patients were significantly lower compared to healthy controls. The decrease in SUB in cases of stroke indicates that the organism tends to conserve energy and minimize metabolism to survive. Since calorie restriction in animals leads to a decrease in the levels of SUB, it has been suggested to be related to conserving energy and minimizing metabolism to survive[55]. Dadmanesh et al[56] reported a relationship between SUB and coronary artery disease (CAD) and atherosclerosis and found significantly lower circulating SUB

concentrations in patients with CAD and DM. There is a physio-pathological similarity between CAD and cerebral ischemia. Therefore, low SUB levels found in cerebral ischemia and low SUB levels detected in CAD indirectly support our current results[57]. In addition, cerebral ischemia may cause irreversible cellular damage[58], resulting in a decrease in SUB concentrations in these diseases. Furthermore, this study demonstrated a correlation between the glucose and SUB levels of SAH, CI and ICH patients. However, contrary to our results, Lee et al[59] reported no significant relationship between SUB and glucose concentrations. This difference may probably be due to the physiopathology of the disease. In this study, the absence of oxygen and nutrients (including glucose) needed by the brain due to the occlusion of cerebral vessels in cerebral ischemia may be due to glucose pooling in the circulation and also the depletion of glycogen stores due to cerebral ischemia stress[60,61]. The participants included in this study had no known history of diabetes.

Moreover, the ALA levels of SAH, CI and ICH patients in this study were significantly lower compared to healthy controls. Ischemia is caused by deficient nutrients and oxygen supply to the brain due to the occlusion or narrowing of the vessels supplying the brain[62]. The possible reason for the high ALA levels in SAH, CI and ICH patients may be the occlusion of the cerebral vessels or the compensatory increase in the amount of circulating ALA to protect the brain tissue from ischemia-reperfusion injury. A study[63] reported that the administration of ALA to rats protected them from myocardial ischemia-reperfusion injury by activating C-Jun N-terminal kinase (JNK) and inhibiting nuclear factor-kappa B (NF-κB). In addition, ALA receptor (MrgD) is located in the nuclear regions of cell membrane, cytoplasm, perinuclear and brain cells[38]; therefore, an increase in ALA secondary to SAH, CI and ICH may have acted as an armor to protect brain cells from harmful effects by exhibiting antifibrotic and anti-inflammatory effects[37]. A study[64] reported that the administration of ALA protected brain cells from damage, excitotoxicity and cell death. These protective effects have been reported to disappear when the ALA receptor is blocked[38]. Moreover, the comparison of the SBP and DBP values of SAH, CI and ICH patients in our study showed significantly higher levels compared to healthy volunteers. The possible reason for the high ALA values in SAH, CI and ICH patients may be the compensatory increase to control the reported high blood pressure[65]. A study on hypertensive rats reported that the administration of ALA alleviated hypertension and cardiac hypertrophy[35]. ALA dynamically changes during stroke in humans. ALA activation might induce neuroprotection in stroke. Therefore, it is predicted that ALA may have the potential to guide clinical targets for stroke therapies in the future.

The comparison of ASP and glucose levels of SAH, CI, and ICH patients in this study revealed significantly higher values compared to the ASP and glucose levels of healthy controls. There is a study in the literature investigating the relationship between cerebral ischemia and asprosin. They found that asprosin level was increased at the beginning of minor ischemic stroke when compared to the control group[66]. Also, increased amounts of asprosin have been reported in ischemic heart disease, which extends credit to our present results[67]. High glucose levels reported in patients with SAH, CI, and ICH indicate impaired glucose homeostasis in these patients[60]. A study[68] on patients with acute stroke and hemorrhage reported increased glucose levels, suggesting that high blood glucose may be an indicator of poor prognosis and high in-hospital mortality. As is understood from here, SAH, CI, and ICH are a cluster of diseases that require strict control of glucose concentrations in patients. Asprosin is a hormone that induces glucose secretion from the liver and protects cells from apoptosis[69]. Reactive oxygen species increase in SAH, CI, and ICH[70]. Therefore, ASP protects brain cells from apoptosis by reducing reactive oxygen species in cases where glucose levels are above the physiological dose. In the light of the available data, we suggest that the possible reason for the increased levels of ASP in SAH, CI, and ICH patients in our study may be due to this.

Limitations

This study has some limitations. First, we have a limited number of subjects. Second, lower MaR-1, SUB, ALA, and higher ASP concentrations in SAH, CI and ICH patients despite the presence of healthy volunteers, it is not exactly known whether the decrease in MaR-1, SUB, ALA concentrations and the increase in ASP concentrations during ischemia are entirely secondary to brain injury necrosis, since the pre-ischemic MaR-1, SUB, ALA and ASP concentrations of the patients could not be determined. Third, the drugs used by the patients were not classified in this study. Medications used by patients may also affect the concentrations of MaR-1, SUB, ALA,

and ASP. Fourth, we attempted to include patients who presented to our hospital at the same time intervals to prevent our results from being affected by the circadian rhythm, but this was very difficult. Because the admission hours of stroke patients to our hospital were untimely. Therefore, not knowing whether our results are affected by the circadian rhythm is another limitation of the study. However, we should immediately point out that there is not yet a study in the literature showing whether MaR-1, SUB, ALA, and ASP have a circadian rhythm.

Conclusions

Despite all the above-mentioned limitations, our study demonstrated decreased MaR-1, SUB, and ALA concentrations and increased ASP concentrations in patients with SAH, CI, and ICH. Low MaR-1, SUB, and ALA and high ASP levels in SAH, CI, and ICH patients can be an indicator of poor prognosis and high in-hospital mortality, as well as an indicator of the etiophysiopathology of these diseases.

Conflict of Interest

The authors have declared that no conflicts of interest exist.

Ethics Approval

This study was conducted after obtaining the approval of the Clinical Research and Ethics Committee (issue 9/41/ dated 6/7/ 2022).

Informed Consent

Written informed consent was obtained from all the patients included in the study.

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