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Review Article

Potential Biomarkers for Vasospasm and Clinical Outcome after Aneurysmal Subarachnoid Hemorrhage

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Abstract

Aneurysmal subarachnoid hemorrhage (SAH) and its sequela is a devastating disease process often leading to poor clinical outcome. The development of cerebral vasospasm (CV) and other delayed ischemic neurologic deficits (DINDs) determine the prognosis of patients after SAH. As a result, several studies have investigated the etiology of CV and DINDs in order to establish biological biomarkers that are clinically relevant for diagnostic and/or monitoring purposes. Despite our knowledge of the disease progression and our understanding of the role of inflammation, endothelial and vascular smooth muscle cell dysfunction, brain injury, and genetics, no candidate biomarker is routinely being used in the clinic. We review the current literature pertaining to biomarkers of CV and their clinical utility in the management of SAH patients.

Keywords: Biomarkers; Delayed ischemic neurological deficits; Cerebral vasospasm; Subarachnoid hemorrhage; Genetic markers

Introduction

Aneurysmal subarachnoid hemorrhage (SAH) remains a devastating disease, with a majority of patients suffering a poor outcome. Despite advances in microsurgical and endovascular therapies, patients are frequently left with disabling neurologic deficits, resulting in a diminished quality of life and a loss of independence. For those that survive the initial aneurysm rupture, a significant percentage of persistent focal and/or cognitive deficits are the result of cerebral vasospasm (CV) and delayed ischemic neurologic deficits (DINDs) [1]. CV, which occurs in 70% of all SAH patients, is clinically significant in approximately 30% of the population and is the most serious complication in those surviving the first 24 hours following aneurysm rupture [2]. Importantly, CV accounts for a disproportionately high morbidity and mortality among young persons. Although the etiology of CV remains unclear, several studies have suggested that inflammation, endothelial dysfunction, response to brain injury, and genetic markers all play a role in CV pathogenesis. Despite our knowledge of the disease progression, there are no established biological biomarkers currently being used in the clinic for diagnostic or monitoring purposes. We review the current literature pertaining to biomarkers of CV and their clinical utility in the management of SAH patients.

Inflammation

Aneurysm rupture results in the forceful entry of arterial blood into the subarachnoid space, leading to the circulation of erythrocytes and plasma throughout the cerebrospinal fluid (CSF). With time, these red blood cells are lysed, thereby creating a cytotoxic environment rich in free hemoglobin (Hgb) and the products of heme breakdown [3]. Through a series of complex cellular and molecular events, these byproducts of erythrocyte lysis trigger an immune response [4]. This inflammation cascade involves accumulation of immune cells through the expression of specific intercellular adhesion molecules (ICAMs), cytokine production, immunoglobulin and complement activation, and various signaling pathways [5]. As a result, the post-SAH inflammatory response has become a target of interest in identifying the molecular and cellular biomarkers of CV.

Intercellular Adhesion Molecules

ICAMs play a critical role in the inflammatory response to injury, thereby making them potentially attractive markers for the prediction of CV in the setting of post-SAH inflammation [6]. Multiple animal models have identified leukocyte-endothelial cell interactions to play a role in the pathogenesis of CV [7, 8]. Three families of ICAMs in particular, the selectins, integrins, and the immunoglobulin super family, may serve as potential clinically relevant biomarkers.

Although ICAMs have been shown to be upregulated following SAH [9-14], conflicting studies on its role in CV and DINDs have been reported. Polin et al. found significantly elevated CSF levels of ICAM-1, vascular cell adhesion molecule-1 (VCAM-1), and E-selectin after SAH compared with control patients [9]. Interestingly, in the same study, E-selectin was the only adhesion molecule significantly elevated in the CSF of patients who later developed CV compared with those patients with uncomplicated SAH [9]. Kaynar et al. reported that ICAM-1 and VCAM-1 levels in the CSF and serum of patients with SAH were significantly elevated compared with control patients with hydrocephalus [10]. Nissen et al. reported no significant difference in serum concentration in several adhesion molecules including ICAM-1, VCAM-1, platelet endothelial cell adhesion molecule (PECAM-1), and E-selectin in patients who developed DINDs after SAH compared with those who did not [14]. However, the authors were able to show significant levels of serum P-selectin concentrations and lower levels of L-selectin concentrations in patients with DINDs [14]. Furthermore, investigating ICAM-1 levels, Mocco et al. and Mack et al. were both able to demonstrate increased soluble ICAM-1 levels in patients with SAH compared with control patients. In their studies, patients who later developed CV showed significant levels of ICAM-1 during the perivasospasm period (e.g., first 2 weeks) [11, 12], with

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delayed ICAM-1 elevation (e.g., peak levels 8-12 days after SAH) correlating with poor clinical outcome [11].

The clinical utility of the two major integrins facilitating cell-cell adhesion and interaction, lymphocyte function-associated antigen 1 (LFA-1) and macrophage-1 antigen (Mac-1), has yet to be evaluated in humans. However, monoclonal antibodies against these integrin family members using various SAH animal models have demonstrated a decrease in inflammatory response and CV and suggest potential candidate biomarkers. By blocking leukocyte migration into the subarachnoid space, CV was prevented in rats [7], rabbits [15], and cynomolgus monkeys [16]. Remarkably, these studies suggest that leukocytes play an important role in the pathogenesis of CV, since CV was prevented in the primate model despite the unaltered presence of hemoglobin in the subarachnoid space [16].

Cytokines

In response to SAH, activation of microglia and astrocytes result in the proliferation and the secretion of three important cytokines: tumor necrosis factor-α (TNF-α), interleukin-1-beta (IL-1β), and interleukin-6 (IL-6) [17]. Multiple authors have reported the detection of these cytokines in the CSF of SAH patients [18-24]. Using cerebral microdialysis to measure CSF TNF-α levels, Hanafy et al. demonstrated a progressive rise in brain interstitial TNF-α levels 4 – 6 days after SAH [25]. Mathiesen et al. reported that patients with poor outcome after SAH had elevated TNF-α levels in their CSF on post-SAH days 4 – 10 [19]. In addition, studies by Fassbender et al. [23] and Chou et al. [24] also linked TNF-α levels with poor clinical outcome. Specifically, Chou et al. determined that elevated serum TNF-α levels 2-3 days after SAH were associated with a poor clinical outcome three months post-hemorrhage. Interestingly, in the same study, TNF-α levels were not associated with vasospasm [24].

Several studies have shown increased IL-6 levels in CSF following SAH [18, 21, 22, 26]. Patients with CV had significantly elevated IL-6 levels compared to patients without CV [20, 26, 27]. In addition, numerous studies have identified significantly elevated CSF levels of IL-6 in the acute phase (days 0-6) following SAH [18, 20-22, 26, 27]. As a result, CSF IL-6 concentration early in the disease progression, may predict CV development following SAH [26]. High concentrations of CSF IL-6 have also been observed in patients who developed DINDs, suggesting IL-6 CSF concentration as a potential predictor of clinically significant CV [28].

Studies investigating levels of IL-1β in SAH patients are inconsistent. Whereas, several studies found no detectable IL-1β in serum or CSF of SAH patients [21, 29], Hendryk et al. reported a significant increase in CSF IL-1β in SAH patients who developed CV and DINDs [22]. IL-1 receptor antagonist (IL-1ra), a potent inhibitor of IL-1, has been shown to be elevated in the CSF of patients after SAH [30] and may be associated with delayed ischemic events and poor clinical outcome [19].

The elevation of additional cytokines following SAH has been observed, however, the significance of these molecules as they relate to CV has yet to be determined. Interleukin-8 (IL-8) has been shown to be elevated in the CSF of patients with SAH [20, 21, 29], although Gaetani et al. found no association with CV [20]. The levels of monocyte chemoattractant protein-1 (MCP-1) were found to be significantly higher in patients with SAH than in those with unruptured aneurysms [20, 31]. Although both studies found higher MCP-1 levels in CSF following SAH, the two studies conflict in determining an association with CV. Kim et al. found a significant elevation of MCP-1 levels in patients with angiographically confirmed vasospasm [31]. Conversely, Gaetani et al. found no significant difference in MCP-1 levels between patients with or without CV [20]. Finally, in a small study conducted by Mathiesen et al., the authors identified increased neopterin concentrations in both the serum and CSF of patients suffering from DINDs compared to uncomplicated SAH cases [32].

C-reactive Protein

C-reactive protein (CRP) is a sensitive inflammatory marker that has been studied in relation to cardiovascular diseases [33, 34]. CRP is synthesized by hepatocytes in response to several cytokines including IL-1, IL-6, and TNF-α [35]. As mentioned above, these cytokines have been shown to be associated with CV pathogenesis and are currently being evaluated as candidate biomarkers. Romero et al. demonstrated higher CRP serum levels following SAH to be associated with worse clinical outcomes and neurologic deficits [36]. CRP levels were significantly elevated in the early stages (days 3-7) of disease progression, making CRP a potentially attractive clinically relevant marker for the early identification of those at risk for CV and DINDs [36].

Myeloperoxidase (MPO)

Myeloperoxidase (MPO) is a liposomal enzyme released by leukocytes, particularly by activated neutrophils, in response to a stimulus. Several studies have demonstrated a correlation between serum MPO and risk of myocardial infarction in patients with coronary artery disease [37-39]. Furthermore, serum MPO has been shown to have predictive power in evaluating prognosis in patients following an acute myocardial infarction [40-42].

Given the association between MPO levels and myocardial ischemic events, Lim and colleagues evaluated MPO as a potential biomarker of CV [43]. Serum MPO levels were elevated in SAH patients, compared to patients with unruptured aneurysms. In the same study, elevated serum MPO correlated with clinically significant CV in SAH patients. Furthermore, elevated MPO levels preceded or occurred on the day of symptomatic CV onset in the majority of patients. Based on these results, Lim and colleagues concluded that inflammation played an important role in CV. They also concluded that many of the SAH patients who did not show clinically evident CV had a subclinical level of vasospasm occurring, which in turn caused their MPO levels to rise compared to those patients with unruptured aneurysms [43]. As a result, this early rise in serum MPO may be a viable marker for detecting CV prior to the onset of symptomatology [43].

Complement and Circulating Immune Complexes

There is strong clinical evidence to support complement and circulating immune complexes (CIC) as potential biomarkers for CV. Pellettieri et al. observed that patients with radiographic and/or clinical CV had a significantly higher frequency (52%) of CIC compared to SAH patients without CV (9%) [44]. Follow-up data

confirmed this association and determined that CIC levels during the first week after SAH correlated with CV [45]. Another study also determined that CIC levels were associated with CV and poor clinical outcome [46]. In addition, complement component C3d has been shown to be associated with CV [46] and C3a and C4a have been reported to be associated with DINDs [47]. In contrast, Kawano et al. reported a decrease in levels of CH50, C3, and C4 in patients who developed CV and DINDs [48]. Finally, the lectin complement pathway (LCP) has recently been shown to be activated in patients after SAH and has been linked to SAH severity and development of CV [49].

Endothelial and Vascular Smooth Muscle Cell Dysfunction

Endothelin

The inflammatory response also results in the release of multiple factors responsible for vascular smooth muscle cell (VSMC) contraction [50]. Endothelin (ET) is one of the most potent vasoconstrictors known [51] and has been investigated in relation to SAH and CV. ET has been measured in the CSF and plasma of patients with SAH using a variety of methods. There are conflicting studies on ET levels in CSF and plasma of SAH patients and their relationship to the development of CV and DINDs [52-61]. Kessler et al. reported a significant rise in ET levels in the CSF, but not in the plasma of patients with SAH who developed CV [53]. Additional studies have also found elevated ET CSF levels to correlate with poor clinical outcome [54, 55, 58]. Interestingly, Mascia et al. found high CSF ET levels in patients with a poor neurological condition unrelated to CV. In fact, the authors demonstrated low ET levels in patients with clinically significant vasospasm. The authors of the study concluded that the rise in CSF ET levels may be the result of severe neuronal damage regardless of mechanism (e.g., vasospasm or primary hemorrhagic event) [54]. Another study also determined that the rise in CSF ET levels appear to be the result of cerebral ischemia rather than the result of CV [59].

Oxidative stress

Nitric oxide (NO) is a signaling molecule involved in numerous cellular functions including regulating vascular tone. As a potent vasodilator, NO and NO-containing compounds counteract the vasoconstricting effects of ET [62]. During the first 24 hours following SAH, NO levels fall resulting in constriction of the cerebral vasculature [63]. Temporal changes in CSF nitrite/nitrate (NOx) levels in patients after SAH have been studied with variable results [64, 65]. For instance, Jung et al. and Ramesh et al. found lower NOx levels in patients who developed CV compared to those patients who did not develop CV [66, 67], while Petzold et al. reported higher NOx levels in patients with SAH compared to controls [68]. There is also inconsistency regarding NOx levels and neurologic outcome. Whereas Rejdak et al. found that patients with good clinical outcome had significantly lower CSF NOx levels compared with those with worse clinical outcome [69], Lin et al. reported no correlation between CSF NOx levels and poor clinical outcome in SAH patients [70]. Measuring plasma NOx levels, Ramesh et al. demonstrated that patients with worse clinical outcome had significantly lower NOx levels compared to controls [67]. Adding to the discrepancy is the report by Staalso et al. in which the authors found that temporal changes in NOx levels were dependent on the World Federation of Neurological Societies SAH grade. Initially, the NOx levels were 45% higher in the first 5 days in poor grade patients compared to grade 1 patients, however, on day 11 to 16, the NOx level in poor grade patients declined to below grade 1 patients [71].

Asymmetrical dimethylarginine (ADMA) is an endogenous inhibitor of several nitric oxide synthase (NOS) family members. CSF ADMA levels seem to correlate with development of CV in both animal [72] and human studies [66, 73]. While CSF ADMA levels remained unchanged in patients with SAH who did not develop CV, Jung et al. reported an increase in CSF ADMA levels in those patients who developed CV 3 – 9 days after SAH. These levels then decreased gradually between days 12 – 21 [66]. Similar to ADMA levels in the CSF, plasma ADMA levels were found to increase over the first week after SAH [74]. In addition to studying NOx levels, Staalso et al. also reported that low plasma arginine/ADMA ratios predict mortality after SAH [71].

Additional mediators of the oxidative stress response have been investigated as potential biomarkers of SAH and CV. The superoxide dismutase family (SOD), is downregulated following SAH [75] while malondialdehyde (MDA), which is increased following SAH, has been demonstrated to be higher in SAH patients with poor clinical outcome [75, 76]. Another antioxidant system that utilizes glutathione peroxidase, which is involved in reducing lipid and hydrogen peroxide, appears to increase in activity but not concentration following SAH [77, 78]. Increased evidence of oxidative stress was observed in the CSF of patients with CV despite the increased activity of glutathione peroxidase, suggesting high reactive oxygen species or the antioxidant pathways may be involved in the pathogenesis of vasospasm [78].

Neuropeptides

Neuropeptides have been evaluated in SAH and CV pathogenesis due to their vascular tone properties. However, inconsistent results in the levels of neutropeptides detected in patients with SAH have led to controversy surrounding this topic. Varying levels of calcitonin gene related peptide (CGRP), substance P, vasoactive intestinal peptide (VIP) and neuropeptide Y (NPY) have all been reported by various investigators with no clear consensus on an association [50]. Juul et al. reported high levels of CGRP in SAH patients compared to controls and concluded that this increase may be a compensatory mechanism to avoid CV by dilating the cerebral vessels [79]. However, Edvinsson et al. evaluated CGRP levels in SAH patients and demonstrated in two separate studies that lower levels of CGRP levels were found in SAH patients compared to controls [80, 81]. Similar to these results, investigators studying VIP and substance P using human studies and animal experiments have also demonstrated a gradual reduction in these neuropeptides [79, 82]. Although Hara et al. demonstrated a clear reduction in VIP and substance P in rats, the reduction of these neuropeptides in monkeys with SAH was not as clear, since there was also a reduction observed in the sham monkeys [82]. Based on these animal results, there is no consistent evidence for the reduction in these neuropeptides. Furthermore, in the aforementioned studies evaluating CGRP, Juul et al. and Edvinsson et al. also investigated levels of VIP and substance P and found no significant differences in levels between SAH patients and controls [79, 81]. Finally, although

there are conflicting reports on levels of NPY in SAH patients [83, 84], two recent studies demonstrated higher levels of NPY in SAH patients compared to controls [85] with higher levels found in patients with CV than in those patients without CV [86].

Another neuropeptide, adrenomedullin, has been shown to be elevated in SAH patients and is predictive of neurological outcome [87-90]. However, there are inconclusive results for adrenomedullin levels and development of CV with Kikumoto et al. and Fujioka et al. reporting no association of plasma adrenomedullin levels with CV, while Wijdicks et al. reporting elevated plasma adrenomedullin levels 5 days after SAH in patients who developed CV [87, 88, 91]. Interestingly, Fujioka et al. demonstrated that CSF adrenomedullin levels may be associated with CV [91].

Although secreted by the heart in response to excessive stretching of cardiomyocytes, Brain natriuretic peptide (BNP) has been shown to be elevated in SAH patients and correlate with clinical course including developing CV and DINDs [92-95]. Interestingly, Taub et al. reported high BNP levels associated with cerebral infarction, and in fact, levels were more prominent in patients without angiographic vasospasm [96].

Brain Injury

Cellular damage occurs as a consequence of SAH and its sequela, whereby various factors are released into the subarachnoid space, many of which may serve as potential candidate biomarkers. Under normal physiological conditions, concentrations of these factors are typically negligible in both the CSF and serum. Two of these brain injury factors that have been investigated for their association with SAH pathogenesis are S100B, a protein synthesized by astrocytes and Schwann cells, and neuron-specific enolase (NSE), an enzyme synthesized by neurons. Similar to other candidate biomarkers mentioned previously, there are inconclusive results regarding S100B and NSE as biomarkers for CV. While several studies have validated S100B levels as a predictor of bad clinical outcome [97-101], the predictive power of S100B for development of CV is inconsistent, as Mortiz et al. and Amiri et al. reported no association [97, 102], whereas Oertel et al. reported lower S1000B levels in SAH patients who developed CV [98]. An increase in NSE levels follows SAH; however, there appears to be no association with CV [97, 98, 101].

Other brain injury markers investigated for their link to SAH and CV include glial fibrillary acidic protein (GFAP), neurosin or kallikrein-related peptidase 6 (KLK-6), neurofilaments (NF), and ubiquitin C hydrolase 1 (UCHL1). Temporal changes are vital in using GFAP as a potential biomarker with several studies reporting increased levels within 1-6 hours after onset of SAH but decreasing later in disease progression [103]. Decreased serum levels of KLK-6 were found in patients with SAH, especially in those patients who succumbed to the disease [104]. Neurofilaments and phosphorylated forms of NF are increased in SAH patients and seem to correlate with poor clinical outcome [68, 105-107]. Finally, Lewis et al. reported that UCHL1 levels measured 10 days after a SAH were predictive of neuronal loss and poor clinical outcome [108].

Genetic Biomarkers

Several genetic markers have been reported to be associated with SAH and CV. Polymorphisms within the endothelial nitric oxide synthase (eNOS) gene (e.g., intron 4 27-base pair variable-number-tandem-repeat (27 VNTR) and the promoter single-nucleotide-polymorphism (-786T>C SNP)) have been shown to be associated with SAH and CV. The role of the T and C alleles and their association with CV remains unclear. Starke et al. reported that patients with the T allele of eNOS were more likely to develop severe CV [109]. However, Ko et al. and Khurana et al. reported that the C allele of eNOS was associated more with developing CV [110, 111]. The eNOS 27 VNTR polymorphism predicts susceptibility to intracranial aneurysm rupture [110] but is not associated with CV [111]. Another polymorphism that has been implicated as a risk factor for SAH is (-308 G<A SNP) in the TNF-α gene [112]. Finally, patients with the haptoglobin 2-2 phenotype had a significantly greater risk for developing CV than those with other haptoglobin phenotypes. Further, the haptoglobin 2-2 phenotype may predict clinical outcome [113, 114].

Miscellaneous Markers

Several additional molecules have been investigated as potential biomarkers for predicting risk for SAH or developing CV. Glucose cerebral metabolism and a calculated metabolic ratio (MR) were evaluated which demonstrated that the MR is a reliable indicator for risk of poor neurological outcome after SAH [115]. Apolipoprotein E (ApoE) has been reported to be lower in the CSF of patients with SAH compared with controls. In addition, CSF ApoE levels appear to correlate with neurological outcome [116]. Adiponectin levels were found to be lower in SAH patients [117, 118] and lower adiponectin levels may be associated with the development of delayed cerebral ischemia [118]. Zanier et al. studied the relationship between heart-fatty acid-binding protein (H-FABP) and tau protein levels with severity and clinical outcome in SAH patients. They concluded that both H-FABP and tau protein levels correlated with the extent of brain ischemia, occurrence of CV, and neurological outcome [119]. Investigating alpha-II-spectrin breakdown products (SBDP), Lewis et al. found an increase in CSF SBDP concentration up to 12 hours before the onset of CV [120]. YKL-40 levels in both the CSF and serum of SAH patients were elevated compared to controls [121, 122], although there was no correlation found between YKL-40 levels and development of CV [121]. Although Isman et al. reported observing elevated CSF chitotriosidase levels on days 5 and 7 after SAH; the authors did not find any correlation with chitotriosidase levels and CV or neurological outcome [123]. Serum magnesium levels were investigated in relationship to CV and clinical outcome after SAH with studies identifying no relationship [124, 125]. Finally, matrix metalloproteinases (MMPs) have the potential to offer an early diagnostic biomarker in the setting of CV after SAH [126].

Conclusion

While numerous biomarkers have been investigated for their predictive value in SAH and CV, there is no biomarker that is routinely used in the clinic. Until then, a better understanding of disease pathogenesis is needed before concise and robust biomarkers are identified and translated into clinical practice. With the current candidate biomarkers outlined in this review, additional studies evaluating the utility and effectiveness of these biological biomarkers in a prospective clinical trial is warranted.

References

1. Pluta RM, Hansen-Schwartz J, Dreier J, Vajkoczy P, Macdonald RL, Nishizawa S, et al. Cerebral vasospasm following subarachnoid hemorrhage: time for a new world of thought. Neurol res. 2009; 31: 151-158.
2. Kassell NF, Sasaki T, Colohan AR, Nazar G. Cerebral vasospasm following aneurysmal subarachnoid hemorrhage. Stroke. 1985; 16: 562-572.
3. Ascenzi P, Bocedi A, Visca P, Altruda F, Tolosano E, Beringhelli T, et al. Hemoglobin and heme scavenging. IUBMB Life. 2005; 57: 749-759.
4. Sercombe R, Dinh YR, Gomis P. Cerebrovascular inflammation following subarachnoid hemorrhage. Jpn J Pharmacol. 2002; 88: 227-249.
5. Dumont AS, Dumont RJ, Chow MM, Lin CL, Calisaneller T, Ley KF, et al. Cerebral vasospasm after subarachnoid hemorrhage: putative role of inflammation. Neurosurgery. 2003; 53: 123-133.
6. Gallia GL, Tamargo RJ. Leukocyte-endothelial cell interactions in chronic vasospasm after subarachnoid hemorrhage. Neurol res. 2006; 28: 750-758.
7. Clatterbuck RE, Oshiro EM, Hoffman PA, Dietsch GN, Pardoll DM, Tamargo RJ. Inhibition of vasospasm with lymphocyte function-associated antigen—1 monoclonal antibody in a femoral artery model in rats. J Neurosurg. 2002; 97: 676-682.
8. Sills AK Jr, Clatterbuck RE, Thompson RC, Cohen PL, Tamargo RJ. Endothelial cell expression of intercellular adhesion molecule 1 in experimental posthemorrhagic vasospasm. Neurosurgery. 1997; 41: 453-460.
9. Polin RS, Bavbek M, Shaffrey ME, Billups K, Bogaev CA, Kassell NF, et al. Detection of soluble E-selectin, ICAM-1, VCAM-1, and L-selectin in the cerebrospinal fluid of patients after subarachnoid hemorrhage. J Neurosurg. 1998; 89: 559-567.
10. Kaynar MY, Tanriverdi T, Kafadar AM, Kacira T, Uzun H, Aydin S, et al. Detection of soluble intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in both cerebrospinal fluid and serum of patients after aneurysmal subarachnoid hemorrhage. J Neurosurg. 2004; 101: 1030-1036.
11. Mack WJ, Mocco J, Hoh DJ, Huang J, Choudhri TF, Kreiter KT, et al. Outcome prediction with serum intercellular adhesion molecule-1 levels after aneurysmal subarachnoid hemorrhage. J Neurosurg. 2002; 96: 71-75.
12. Mocco J, Mack WJ, Kim GH, Lozier AP, Laufer I, Kreiter KT, et al. Rise in serum soluble intercellular adhesion molecule-1 levels with vasospasm following aneurysmal subarachnoid hemorrhage. J Neurosurg. 2002; 97: 537-541.
13. Kim JH, Yi HJ, Ko Y, Kim YS, Kim DW, Kim JM. Effectiveness of papaverine cisternal irrigation for cerebral vasospasm after aneurysmal subarachnoid hemorrhage and measurement of biomarkers. Neurol Sci. 2014; 35: 715-722.
14. Nissen JJ, Mantle D, Gregson B, Mendelow AD. Serum concentration of adhesion molecules in patients with delayed ischaemic neurological deficit after aneurysmal subarachnoid haemorrhage: the immunoglobulin and selectin superfamilies. J Neurol Neurosurg Psychiatry. 2001; 71: 329-333.
15. Pradilla G, Wang PP, Legnani FG, Ogata L, Dietsch GN, Tamargo RJ. Prevention of vasospasm by anti-CD11/CD18 monoclonal antibody therapy following subarachnoid hemorrhage in rabbits. J Neurosurg. 2004; 101: 88-92.
16. Clatterbuck RE, Gailloud P, Ogata L, Gebremariam A, Dietsch GN, Murphy KJ, et al. Prevention of cerebral vasospasm by a humanized anti-CD11/CD18 monoclonal antibody administered after experimental subarachnoid hemorrhage in nonhuman primates. J Neurosurg. 2003; 99: 376-382.
17. McKeating EG, Andrews PJ. Cytokines and adhesion molecules in acute brain injury. Br J Anaesth. 1998; 80: 77-84.
18. Mathiesen T, Andersson B, Loftenius A, von Holst H. Increased interleukin-6 levels in cerebrospinal fluid following subarachnoid hemorrhage. J Neurosurg. 1993; 78: 562-567.
19. Mathiesen T, Edner G, Ulfarsson E, Andersson B. Cerebrospinal fluid interleukin-1 receptor antagonist and tumor necrosis factor-alpha following subarachnoid hemorrhage. J Neurosurg. 1997; 87: 215-220.
20. Gaetani P, Tartara F, Pignatti P, Tancioni F, Rodriguez y Baena R, De Benedetti F. Cisternal CSF levels of cytokines after subarachnoid hemorrhage. Neurol Res. 1998; 20: 337-342.
21. Osuka K, Suzuki Y, Tanazawa T, Hattori K, Yamamoto N, Takayasu M, et al. Interleukin-6 and development of vasospasm after subarachnoid haemorrhage. Acta Neurochir (Wien). 1998; 140: 943-951.
22. Hendryk S, Jarzab B, Josko J. Increase of the IL-1 beta and IL-6 levels in CSF in patients with vasospasm following aneurysmal SAH. Neuro Endocrinol Lett. 2004; 25: 141-147.
23. Fassbender K, Hodapp B, Rossol S, Bertsch T, Schmeck J, Schütt S, et al. Inflammatory cytokines in subarachnoid haemorrhage: association with abnormal blood flow velocities in basal cerebral arteries. *J Neurol, Neurosurg Psychiatry*. 2001; 70: 534-537.
24. Chou SH-Y, Feske SK, Atherton J, Konigsberg RG, De Jager PL, Du R, et al. Early Elevation of Serum Tumor Necrosis Factor-a Is Associated With Poor Outcome in Subarachnoid Hemorrhage. J Investig Med. 2012; 60: 1054-1058.
25. Hanafy KA, Grobelny B, Fernandez L, Kurtz P, Connolly ES, Mayer SA, et al. Brain interstitial fluid TNF-a after subarachnoid hemorrhage. J Neurol Sci. 2010; 291: 69-73.
26. Schoch B, Regel JP, Wichert M, Gasser T, Volbracht L, Stolke D. Analysis of intrathecal interleukin-6 as a potential predictive factor for vasospasm in subarachnoid hemorrhage. Neurosurgery. 2007; 60: 828-836.
27. Ni W, Gu YX, Song DL, Leng B, Li PL, Mao Y. The relationship between IL-6 in CSF and occurrence of vasospasm after subarachnoid hemorrhage. Acta Neurochir Suppl. 2011; 110: 203-208.
28. Kwon KY, Jeon BC. Cytokine levels in cerebrospinal fluid and delayed ischemic deficits in patients with aneurysmal subarachnoid hemorrhage. J Korean Med Sci. 2001; 16: 774-780.
29. Kikuchi T, Okuda Y, Kaito N, Abe T. Cytokine production in cerebrospinal fluid after subarachnoid haemorrhage. Neurol Res. 1995; 17: 106-108.
30. Gruber A, Rössler K, Graninger W, Donner A, Illievich UM, Czech T. Ventricular Cerebrospinal Fluid and Serum Concentrations of sTNFR-I, IL-1ra, and IL-6 After Aneurysmal Subarachnoid Hemorrhage. J Neurosurg Anesthesiol. 2000; 12: 297-306.
31. Kim GH, Kellner CP, Hahn DK, Desantis BM, Musabbir M, Starke RM, et al. Monocyte chemoattractant protein-1 predicts outcome and vasospasm following aneurysmal subarachnoid hemorrhage. J Neurosurg. 2008; 109: 38-43.
32. Mathiesen T, Fuchs D, Wachter H, von Holst H. Increased CSF neopterin levels in subarachnoid hemorrhage. J Neurosurg. 1990; 73: 69-71.
33. Koenig W, Sund M, Fröhlich M, Fischer HG, Löwel H, Döring A, et al. C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. Circulation. 1999; 99: 237-242.
34. Mendall MA, Patel P, Ballam L, Strachan D, Northfield TC. C reactive protein and its relation to cardiovascular risk factors: a population based cross sectional study. BMJ. 1996; 312: 1061-1065.
35. Baumann H, Gauldie J. The acute phase response. Immunol Today. 1994; 15: 74-80.
36. Romero FR, Cataneo DC, Cataneo AJ. C-reactive protein and vasospasm after aneurysmal subarachnoid hemorrhage. Acta Cir Bras. 2014; 29: 340-345.
37. Cavusoglu E, Ruwende C, Eng C, Chopra V, Yanamadala S, Clark LT, et al. Usefulness of baseline plasma myeloperoxidase levels as an independent predictor of myocardial infarction at two years in patients presenting with acute coronary syndrome. Am J Cardiol. 2007; 99: 1364-1368.
38. Brennan ML, Penn MS, Van Lente F, Nambi V, Shishehbor MH, Aviles RJ, et al. Prognostic value of myeloperoxidase in patients with chest pain. N Engl J Med. 2003; 349: 1595-1604.

39. Meuwese MC, Stroes ESG, Hazen SL, van Miert JN, Kuivenhoven JA, Schaub RG, et al. Serum Myeloperoxidase Levels Are Associated With the Future Risk of Coronary Artery Disease in Apparently Healthy Individuals: The EPIC-Norfolk Prospective Population Study. J Am Col Cardiol. 2007; 50: 159-165.

40. Khan SQ, Kelly D, Quinn P, Davies JE, Ng LL. Myeloperoxidase aids prognostication together with N-terminal pro-B-type natriuretic peptide in high-risk patients with acute ST elevation myocardial infarction. Heart. 2007; 93: 826-831.

41. Mocatta TJ, Pilbrow AP, Cameron VA, Senthilmohan R, Frampton CM, Richards AM, et al. Plasma concentrations of myeloperoxidase predict mortality after myocardial infarction. J Am Coll Cardiol. 2007; 49: 1993-2000.

42. Koch C, Henrich M, Heidt MC. Sequential analysis of myeloperoxidase for prediction of adverse events after suspected acute coronary ischemia. Clin Cardiol. 2014; 37: 744-749.

43. Lim M, Bower R, Wang Y, Sims L, Bower M, Camara-Quintana J, et al. The predictive value of serum myeloperoxidase for vasospasm in patients with aneurysmal subarachnoid hemorrhage. Neurosurg Rev. 2012; 35: 413-419.

44. Pellettieri L, Carlson CA, Lindholm L. Is the vasospasm following subarachnoidal hemorrhage an immunoreactive disease? Experientia. 1981; 37: 1170-1171.

45. Pellettieri L, Nilsson B, Carlsson CA, Nilsson U. Serum immunocomplexes in patients with subarachnoid hemorrhage. Neurosurgery. 1986; 19: 767-771.

46. Ostergaard JR, Kristensen BO, Svehag SE, Teisner B, Miletic T. Immune complexes and complement activation following rupture of intracranial saccular aneurysms. J Neurosurg. 1987; 66: 891-897.

47. Kasuya H, Shimizu T. Activated complement components C3a and C4a in cerebrospinal fluid and plasma following subarachnoid hemorrhage. J Neurosurg. 1989; 71: 741-746.

48. Kawano T, Yonekawa Y. Serum complements as indicator for predicting vasospasm and its severity after aneurysmal subarachnoid hemorrhage. Nihon Geka Hokan. 1990; 59: 189-197.

49. Zanier ER, Zangari R, Munthe-Fog L, Hein E, Zoerle T, Conte V, et al. Ficolin-3-mediated lectin complement pathway activation in patients with subarachnoid hemorrhage. Neurology. 2014; 82: 126-134.

50. Rodríguez-Rodríguez A, Egea-Guerrero JJ, Ruiz de Azúa-López Z, Murillo-Cabezas F. Biomarkers of vasospasm development and outcome in aneurysmal subarachnoid hemorrhage. J Neurol Sci. 2014; 341: 119-127.

51. Yanagisawa M, Kurihara H, Kimura S, Tomobe Y, Kobayashi M, Mitsui Y, et al. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. Nature. 1988; 332: 411-415.

52. Juvela S. Plasma endothelin concentrations after aneurysmal subarachnoid hemorrhage. J Neurosurg. 2000; 92: 390-400.

53. Kessler IM, Pacheco YG, Lozzi SP, de Araújo AS Jr, Onishi FJ de Mello PA. Endothelin-1 levels in plasma and cerebrospinal fluid of patients with cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Surgical Neurology. 2005; 64: S2-S5.

54. Mascia L, Fedorko L, Stewart DJ, Mohamed F, terBrugge K, Ranieri VM, et al. Temporal relationship between endothelin-1 concentrations and cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage. Stroke. 2001; 32: 1185-1190.

55. Thampatty BP, Sherwood PR, Gallek MJ, Crago EA, Ren D, Hricik AJ, et al. Role of Endothelin-1 in Human Aneurysmal Subarachnoid Hemorrhage: Associations with Vasospasm and Delayed Cerebral Ischemia. Neurocritical care. 2011; 15: 19-27.

56. Juvela S. Plasma endothelin and big endothelin concentrations and serum endothelin-converting enzyme activity following aneurysmal subarachnoid hemorrhage. J Neurosurg. 2002; 97: 1287-1293.

57. Shirakami G, Magaribuchi T, Shingu K, Kim S, Saito Y, Nakao K, et al. Changes of endothelin concentration in cerebrospinal fluid and plasma of patients with aneurysmal subarachnoid hemorrhage. Acta Anaesthesiol Scand. 1994; 38: 457-461.

58. Kästner S, Oertel MF, Scharbrodt W, Krause M, Böker DK, Deinsberger W. Endothelin-1 in plasma, cisternal CSF and microdialysate following aneurysmal SAH. Acta Neurochir (Wien). 2005; 147: 1271-1279.

59. Pluta RM, Boock RJ, Afshar JK, Clouse K, Bacic M, Ehrenreich H, et al. Source and cause of endothelin-1 release into cerebrospinal fluid after subarachnoid hemorrhage. J Neurosurg. 1997; 87: 287-293.

60. Seifert V, Löffler BM, Zimmermann M, Roux S, Stolke D. Endothelin concentrations in patients with aneurysmal subarachnoid hemorrhage. Correlation with cerebral vasospasm, delayed ischemic neurological deficits, and volume of hematoma. J Neurosurg. 1995; 82: 55-62.

61. Zimmermann M, Seifert V. Endothelin and subarachnoid hemorrhage: an overview. Neurosurgery. 1998; 43: 863-875.

62. Kolias AG, Sen J, Belli A. Pathogenesis of cerebral vasospasm following aneurysmal subarachnoid hemorrhage: putative mechanisms and novel approaches. J Neurosci Res. 2009; 87: 1-11.

63. Sehba FA, Schwartz AY, Chereshnev I, Bederson JB. Acute decrease in cerebral nitric oxide levels after subarachnoid hemorrhage. *J Cereb Blood Flow Metab*. 2000; 20: 604-611.

64. Lad SP, Hegen H, Gupta G, Deisenhammer F, Steinberg GK. Proteomic Biomarker Discovery in Cerebrospinal Fluid for Cerebral Vasospasm Following Subarachnoid Hemorrhage. J Stroke Cerebrovasc Dis. 2012; 21: 30-41.

65. Jordan JD, Nyquist P. Biomarkers and Vasospasm After Aneurysmal Subarachnoid Hemorrhage. Neurosurg Clin N Am. 2010; 21: 381-391.

66. Jung CS, Oldfield EH, Harvey-White J, Espey MG, Zimmermann M, Seifert V, et al. Association of an endogenous inhibitor of nitric oxide synthase with cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage. J Neurosurg. 2007; 107: 945-950.

67. Ramesh SS, Prasanthi A, Bhat DI, Devi BI, Cristopher R, Philip M. Correlation between plasma total nitric oxide levels and cerebral vasospasm and clinical outcome in patients with aneurysmal subarachnoid hemorrhage in Indian population. J Neurosci Rural Pract. 2014; 5: S22-S27.

68. Petzold A, Rejdak K, Belli A, Sen J, Keir G, Kitchen N, et al. Axonal pathology in subarachnoid and intracerebral hemorrhage. J Neurotrauma. 2005; 22: 407-414.

69. Rejdak K, Petzold A, Sharpe MA, Kay AD, Kerr M, Keir G, et al. Cerebrospinal fluid nitrite/nitrate correlated with oxyhemoglobin and outcome in patients with subarachnoid hemorrhage. J Neurol Sci. 2004; 219: 71-76.

70. Lin CL, Hsu YT, Lin TK, Morrow JD, Hsu JC, Hsu YH, et al. Increased levels of F2-isoprostanes following aneurysmal subarachnoid hemorrhage in humans. Free Radic Biol Med. 2006; 40: 1466-1473.

71. Staalsø JM, Bergström A, Edsen T, Weikop P, Romner B, Olsen NV. Low Plasma Arginine:Asymmetric Dimethyl Arginine Ratios Predict Mortality After Intracranial Aneurysm Rupture. Stroke. 2013; 44: 1273-1281.

72. Jung CS, Iuliano BA, Harvey-White J, Espey MG, Oldfield EH, Pluta RM. Association between cerebrospinal fluid levels of asymmetric dimethyl-L-arginine, an endogenous inhibitor of endothelial nitric oxide synthase, and cerebral vasospasm in a primate model of subarachnoid hemorrhage. J Neurosurg. 2004; 101: 836-842.

73. Jung CS, Lange B, Zimmermann M, Seifert V. The CSF concentration of ADMA, but not of ET-1, is correlated with the occurrence and severity of cerebral vasospasm after subarachnoid hemorrhage. Neurosci Lett. 2012; 524: 20-24.

74. Rodling-Wahlström M, Olivecrona M, Koskinen L-OD, Naredi S, Hultin M. Subarachnoid haemorrhage induces an inflammatory response followed by a delayed persisting increase in asymmetric dimethylarginine. Scand J Clin Lab Invest. 2012; 72: 484-489.

75. Kaynar MY, Tanriverdi T, Kemerdere R, Atukeren P, Gumustas K. Cerebrospinal fluid superoxide dismutase and serum malondialdehyde levels in patients with aneurysmal subarachnoid hemorrhage: preliminary results. Neurol res. 2005; 27: 562-567.

76. Kaneda K, Fujita M, Yamashita S, Kaneko T, Kawamura Y, Izumi T, et al. Prognostic value of biochemical markers of brain damage and oxidative stress in post-surgical aneurysmal subarachnoid hemorrhage patients. Brain Res Bull. 2010; 81: 173-177.

77. Watanabe T, Sasaki T, Asano T, Takakura K, Sano K, Fuchinoue T, et al. Changes in glutathione peroxidase and lipid peroxides in cerebrospinal fluid and serum after subarachnoid hemorrhage--with special reference to the occurrence of cerebral vasospasm. Neurol Med Chir (Tokyo). 1988; 28: 645-649.

78. Pyne-Geithman GJ, Caudell DN, Prakash P, Clark JF. Glutathione peroxidase and subarachnoid hemorrhage: implications for the role of oxidative stress in cerebral vasospasm. Neurol res. 2009; 31: 195-199.

79. Juul R, Hara H, Gisvold SE, Brubakk AO, Fredriksen TA, Waldemar G, et al. Alterations in perivascular dilatory neuropeptides (CGRP, SP, VIP) in the external jugular vein and in the cerebrospinal fluid following subarachnoid haemorrhage in man. Acta Neurochir (Wien). 1995; 132: 32-41.

80. Edvinsson L, Ekman R, Jansen I, McCulloch J, Mortensen A, Uddman R. Reduced levels of calcitonin gene-related peptide-like immunoreactivity in human brain vessels after subarachnoid haemorrhage. Neurosci Lett. 1991; 121: 151-154.

81. Edvinsson L, Juul R, Jansen I. Perivascular neuropeptides (NPY, VIP, CGRP and SP) in human brain vessels after subarachnoid haemorrhage. Acta Neurol Scand. 1994; 90: 324-330.

82. Hara H, Nosko M, Weir B. Cerebral perivascular nerves in subarachnoid hemorrhage. A histochemical and immunohistochemical study. J Neurosurg. 1986; 65: 531-539.

83. Suzuki Y, Sato S, Suzuki H, Namba J, Ohtake R, Hashigami Y, et al. Increased neuropeptide Y concentrations in cerebrospinal fluid from patients with aneurysmal subarachnoid hemorrhage. Stroke. 1989; 20: 1680-1684.

84. Valenzuela RF, Donoso MV, Mellado PA, Huidobro-Toro JP. Migraine, but not subarachnoid hemorrhage, is associated with differentially increased NPY-like immunoreactivity in the CSF. J Neurol Sci. 2000; 173: 140-146.

85. Schebesch KM, Brawanski A, Kagerbauer SM, Martin J, Bele S, Herbst A, et al. The possible role of neuropeptide Y after spontaneous subarachnoid hemorrhage. Acta Neurochir (Wien). 2011; 153: 1663-1668.

86. Schebesch K-M, Brawanski A, Bele S, Schödel P, Herbst A, Bründl E, et al. Neuropeptide Y – an early biomarker for cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Neurol res. 2013; 35: 1038-1043.

87. Kikumoto K, Kubo A, Hayashi Y, Minamino N, Inoue S, Dohi K, et al. Increased Plasma Concentration of Adrenomedullin in Patients with Subarachnoid Hemorrhage. Anesth Analg. 1998; 87: 859-863.

88. Wijdicks EF, Heublein DM, Burnett JC Jr. Increase and uncoupling of adrenomedullin from the natriuretic peptide system in aneurysmal subarachnoid hemorrhage. J Neurosurg. 2001; 94: 252-256.

89. Kubo Y, Koji T, Kashimura H, Otawara Y, Ogawa A, Ogasawara K. Adrenomedullin concentration in the cerebrospinal fluid is related to appetite loss and delayed ischemic neurological deficits after subarachnoid hemorrhage. Neurol res. 2013; 35: 713-718.

90. Cai JY, Chen XD, Ba HJ, Lin JH, Lu C, Chen MH, et al. Identification of plasma adrenomedullin as a possible prognostic biomarker for aneurysmal subarachnoid hemorrhage. Peptides. 2014; 59: 9-13.

91. Fujioka M, Nishio K, Sakaki T, Minamino N, Kitamura K. Adrenomedullin in Patients With Cerebral Vasospasm After Aneurysmal Subarachnoid Hemorrhage. Stroke. 2000; 31: 3079-3083.

92. Sviri GE, Feinsod M, Soustiel JF. Brain natriuretic peptide and cerebral vasospasm in subarachnoid hemorrhage. Clinical and TCD correlations. Stroke. 2000; 31: 118-122.

93. Sviri GE, Shik V, Raz B, Soustiel JF. Role of brain natriuretic peptide in cerebral vasospasm. Acta Neurochir (Wien). 2003; 145: 851-860.

94. McGirt MJ, Blessing R, Nimjee SM, Friedman AH, Alexander MJ, Laskowitz DT, et al. Correlation of Serum Brain Natriuretic Peptide with Hyponatremia and Delayed Ischemic Neurological Deficits after Subarachnoid Hemorrhage. Neurosurgery. 2004; 54: 1369-1374.

95. Nyberg C, Karlsson T, Ronne-Engström E. Predictors of increased cumulative serum levels of the N-terminal prohormone of brain natriuretic peptide 4 days after acute spontaneous subarachnoid hemorrhage. J Neurosurg. 2014; 120: 599-604.

96. Taub P, Fields J, Wu AB, Miss J, Lawton M, Smith W, et al. Elevated BNP is Associated with Vasospasm-Independent Cerebral Infarction Following Aneurysmal Subarachnoid Hemorrhage. Neurocrit Care. 2011; 15: 13-18.

97. Moritz S, Warnat J, Bele S, Graf BM, Woertgen C. The Prognostic Value of NSE and S100B From Serum and Cerebrospinal Fluid in Patients With Spontaneous Subarachnoid Hemorrhage. J Neurosurg Anesthesiol. 2010; 22: 21-31.

98. Oertel M, Schumacher U, McArthur DL, Kästner S, Böker DK. S-100B and NSE: markers of initial impact of subarachnoid haemorrhage and their relation to vasospasm and outcome. J Clin Neurosci. 2006; 13: 834-840.

99. Sanchez-Peña P, Pereira AR, Sourour NA, Biondi A, Lejean L, Colonne C, et al. S100B as an additional prognostic marker in subarachnoid aneurysmal hemorrhage. Crit Care Med. 2008; 36: 2267-2273.

100. Wiesmann M, Missler U, Hagenström H, Gottmann D. S-100 protein plasma levels after aneurysmal subarachnoid haemorrhage. Acta Neurochir (Wien). 1997; 139: 1155-1160.

101. Jung CS, Lange B, Zimmermann M, Seifert V. CSF and Serum Biomarkers Focusing on Cerebral Vasospasm and Ischemia after Subarachnoid Hemorrhage. Stroke Res Treat. 2013; 2013: 560305.

102. Amiri M, Astrand R, Romner B. Can S100B Predict Cerebral Vasospasms in Patients Suffering from Subarachnoid Hemorrhage? Front Neurol. 2013; 4: 65.

103. Petzold A. Glial fibrillary acidic protein is a body fluid biomarker for glial pathology in human disease. Brain Res. 2015; 1600: 17-31.

104. Martínez-Morillo E, Diamandis A, Romaschin AD, Diamandis EP. Kallikrein 6 as a serum prognostic marker in patients with aneurysmal subarachnoid hemorrhage. PLoS One. 2012; 7: e45676.

105. Petzold A, Keir G, Kay A, Kerr M, Thompson EJ. Axonal damage and outcome in subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry. 2006; 77: 753-759.

106. Nylén K, Csajbok LZ, Ost M, Rashid A, Karlsson JE, Blennow K, et al. CSF -neurofilament correlates with outcome after aneurysmal subarachnoid hemorrhage. Neurosci Lett. 2006; 404: 132-136.

107. Lewis SB, Wolper RA, Miralia L, Yang C, Shaw G. Detection of phosphorylated NF-H in the cerebrospinal fluid and blood of aneurysmal subarachnoid hemorrhage patients. J Cereb Blood Flow Metab. 2008; 28: 1261-1271.

108. Lewis SB, Wolper R, Chi YY, Miralia L, Wang Y, Yang C, et al. Identification and preliminary characterization of ubiquitin C terminal hydrolase 1 (UCHL1) as a biomarker of neuronal loss in aneurysmal subarachnoid hemorrhage. J Neurosci Res. 2010; 88: 1475-1484.

109. Starke RM, Kim GH, Komotar RJ, Hickman ZL, Black EM, Rosales MB, et al. Endothelial nitric oxide synthase gene single-nucleotide polymorphism predicts cerebral vasospasm after aneurysmal subarachnoid hemorrhage. J Cereb Blood Flow Metab. 2008; 28: 1204-1211.

110. Khurana VG, Sohni YR, Mangrum WI, McClelland RL, O'Kane DJ, Meyer FB, et al. Endothelial nitric oxide synthase gene polymorphisms predict susceptibility to aneurysmal subarachnoid hemorrhage and cerebral vasospasm. J Cereb Blood Flow Metab. 2004; 24: 291-297.

111. Ko NU, Rajendran P, Kim H, Rutkowski M, Pawlikowska L, Kwok P-Y, et al. Endothelial nitric oxide synthase polymorphism (-786T>C) and increased risk of angiographic vasospasm after aneurysmal subarachnoid hemorrhage. Stroke. 2008; 39: 1103-1108.

112. Fontanella M, Rainero I, Gallone S, Rubino E, Fenoglio P, Valfrè W, et al. Tumor necrosis factor-alpha gene and cerebral aneurysms. Neurosurgery. 2007; 60: 668-672.

113. Leclerc JL, Blackburn S, Neal D, Mendez NV, Wharton JA, Waters MF, et al. Haptoglobin phenotype predicts the development of focal and global cerebral vasospasm and may influence outcomes after aneurysmal subarachnoid hemorrhage. Proc Nati Acad Sci. 2015; 112: 1155-1160.

114. Ohnishi H, Iihara K, Kaku Y, Yamauchi K, Fukuda K, Nishimura K, et al. Haptoglobin Phenotype Predicts Cerebral Vasospasm and Clinical Deterioration after Aneurysmal Subarachnoid Hemorrhage. J Stroke Cerebrovasc. 2013; 22: 520-526.

115. Barcelos G, Tholance Y, Grousson S, Renaud B, Perret-Liaudet A, Dailler F, et al. Outcome of Poor-Grade Subarachnoid Hemorrhage as Determined by Biomarkers of Glucose Cerebral Metabolism. Neurocrit Care. 2013; 18: 234-244.

116. Kay A, Petzold A, Kerr M, Keir G, Thompson E, Nicoll J. Decreased Cerebrospinal Fluid Apolipoprotein E After Subarachnoid Hemorrhage: Correlation With Injury Severity and Clinical Outcome. Stroke. 2003; 34: 637-642.

117. Jernås M, Olsson B, Sjöholm K, Sjögren A, Rudemo M, Nellgård B, et al. Changes in adipose tissue gene expression and plasma levels of adipokines and acute-phase proteins in patients with critical illness. Metabolism. 2009; 58: 102-108.

118. Takeuchi S, Wada K, Otani N, Osada H, Nagatani K, Mori K. Temporal profile of plasma adiponectin level and delayed cerebral ischemia in patients with subarachnoid hemorrhage. J Clin Neurosci. 2014; 21: 1007-1010.

119. Zanier ER, Zoerle T, Fiorini M, Longhi L, Cracco L, Bersano A, et al. Heart-fatty acid-binding and tau proteins relate to brain injury severity and long-term outcome in subarachnoid haemorrhage patients. Br J Anaesth. 2013; 111: 424-432.

120. Lewis SB, Velat GJ, Miralia L, Papa L, Aikman JM, Wolper RA, et al. Alpha-II spectrin breakdown products in aneurysmal subarachnoid hemorrhage: a novel biomarker of proteolytic injury. J Neurosurg. 2007; 107: 792-796.

121. Kacira T, Hanimoglu H, Kucur M, Sanus GZ, Kafadar AM, Tanriverdi T, ey al. Elevated cerebrospinal fluid and serum YKL-40 levels are not associated with symptomatic vasospasm in patients with aneurysmal subarachnoid haemorrhage. J Clin Neurosci. 2008; 15: 1011-1016.

122. Kaynar MY, Tanriverdi T, Kafadar AM, Kacira T, Yurdakul F, Uzun H, et al. YKL-40 levels in the cerebrospinal fluid and serum of patients with aneurysmal subarachnoid hemorrhage: Preliminary results. J Clin Neurosci. 2005; 12: 754-757.

123. Isman FK, Kacira T, Kucur M, Sanus GZ, Atukeren P, Tanriverdi T, et al. Cerebrospinal fluid and serum chitotriosidase levels in patients with aneurysmal subarachnoid haemorrhage: preliminary results. Turk neurosurg. 2007; 17: 235-242.

124. Odom MJ, Zuckerman SL, Mocco J. The role of magnesium in the management of cerebral vasospasm. Neurol Res Int. 2013; 2013: 943914.

125. Collignon F, Friedman J, Piepgras D, Pichelmann M, McIver J, Toussaint LG, III, et al. Serum magnesium levels as related to symptomatic vasospasm and outcome following aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2004; 1: 441-448.

126. Mehta V, Russin J, Spirtos A, He S, Adamczyk P, Amar AP, et al. Matrix Metalloproteinases in Cerebral Vasospasm following Aneurysmal Subarachnoid Hemorrhage. Neurol Res Int. 2013; 2013: 4.

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