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Biomarkers of vasospasm development and outcome in aneurysmal subarachnoid hemorrhage

Ana Rodríguez-Rodríguez, Juan José Egea-Guerrero *, Zaida Ruiz de Azúa-López, Francisco Murillo-Cabezas

NeuroCritical Care Unit, Virgen del Rocío University Hospital, IBiS/CSIC/University of Seville, Seville, Spain

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ABSTRACT

Aneurysmal subarachnoid hemorrhage (SAH) is a neurologic emergency caused by a brain aneurysm burst, resulting in a bleeding into the subarachnoid space. Its incidence is estimated between 4 and 28/10,000 inhabitants and it is the main cause of sudden death from stroke. The prognosis of patients with SAH is directly related to neurological status on admission, to the magnitude of the initial bleeding, as well as to the development of cerebral vasospasm (CVS). Numerous researchers have studied the role of different biomarkers in CVS development. These biomarkers form part of the metabolic cascade that is triggered as a result of the SAH. Hence, among these metabolites we found biomarkers of oxidative stress, inflammation biomarkers, indicators of brain damage, and markers of vascular pathology. However, to the author knowledge, none of these biomarkers has been demonstrated as a useful tool for predicting neither CVS development nor outcome after SAH. In order to reach success on future researches, firstly it should be stated which pathophysiological process is mainly responsible for CVS development. Once this process has been determined, the temporal course of this pathophysiologic cascade should be characterized, and then, perform further studies on biomarkers already analyzed, as well as on new biomarkers not yet studied in the SAH pathology, focusing attention on the temporal course of the diverse metabolites and the sampling time for its quantification.

1. Introduction

Aneurysmal subarachnoid hemorrhage (SAH) is a neurologic emergency caused by a brain aneurysm burst, resulting in a bleeding into the space surrounding the central nervous system (CNS), which is normally filled with cerebrospinal fluid (CSF). The aneurismal SAH accounts for about 80% of all nontraumatic extravasated bleeding into the subarachnoid space [1]. Its incidence is estimated between 4 and 28/10,000 inhabitants and it is the main cause of sudden death from stroke [2]. Despite researcher efforts focused on improving outcome for patients suffering a SAH, the rate of fatal outcome remains high. Approximately 15% of patients die after the aneurysm burst, while 25–50% die within a month of the bleeding. In reference to survivors, 40% of them present disabling sequelae [3–5]. Numerous studies have observed that the prognosis of patients with SAH is directly related to neurological status on admission, stratified according to the Hunt–Hess scale, the World Federation of Neurological Surgeon (WFNS) scale and the Johns Hopkins University Classification [6], as well as the occurrence of delayed ischemia deficit consequence of cerebral vasospasm (CVS) development, related to the magnitude of the initial bleeding on head CT-scan, stratified according to the Fisher scale and the Modified Fisher Scale [2,7]. Nevertheless, the complications that can occur after the initial bleeding are largely responsible for the high morbidity and mortality of SAH [8]. The patocronia of them is well known: hydrocephalus and rebleeding, which occur on the first 24–48 h; and CVS, which takes place from day 4 until the second week. The CVS is characterized by diffuse and long-lasting (more than two weeks) narrowing of arteries. It is estimated that CVS is responsible for neurological deterioration and even for death of 15–20% of SAH patients [3]. Presumably, it is the unique kind of acute cerebral ischemia that might be preventable trough an early detection and implementation of invasive and non-invasive procedures [9]. Up to date, monitoring of this phenomenon is made by clinical examination, transcranial Doppler-sonography records and cerebral arteriography [10–12]. Although numerous researchers have studied the role of different biomarkers in CVS development and SAH outcome, there are currently no established biomarkers for early diagnosis of CVS development or monitoring its progression, tool that would help physicians during treatment decision making.

2. Pathophysiologic cascade

As a consequence of bleeding red blood cells (RBCs) suffer lysis shortly after the injury, resulting in a release of large quantities of free

* Corresponding author at: NeuroCritical Care Unit, Virgen del Rocío University Hospital, IBiS/CSIC/University of Seville, Avda. Manuel Siurot s/n, 41013 Seville, Spain. Tel.: +34 955012582; +34 686638646; fax: +34 955 012582.
E-mail addresses: juanjoegea@hotmail.com, juanj.egea.sspa@juntadeandalucia.es (J.J. Egea-Guerrero).

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hemoglobin (Hgb) into the subarachnoid space, which is extremely toxic [13]. This free Hgb is neutralized, in part, by its high affinity interaction with haptoglobin (Hp), a protein synthesized in the hepatocytes [13]. As a result of bleeding in SAH, a primary immune response is immediately triggered, mediated by macrophages and neutrophils [14,15], which enter the subarachnoid space due to the expression of specific cell adhesion molecules (CAMs) on the luminal surface of endothelial cells, expression upregulated by RBC lysis [16]. These cells phagocyte RBCs and clear free Hgb–Hp complex. After that, these immune system cells remain trapped in the subarachnoid space due to the absence of lymphatic vessels in the CNS and impaired CSF flow caused by the SAH [16,17]. Macrophages and neutrophils die and degranulate within 2 to 4 days after entering the subarachnoid space [18,19], what results in a release of intracellular endothelins (ET) and oxygen free radicals, both molecules responsible for inflammation-induced arteriopathy and arterial vasoconstriction [18–20]. The time course of this process coincides with the temporal pattern of CVS development, fact which leads us to consider the relevance of this first biochemical cascade in the development of CVS. In turn, this process promotes the second immune response or chronic inflammation [21], which has lymphocytes and plasma cells as main effector cells, develops in days or weeks, and can persist for months and years [22,23] (Fig. 1). This secondary or chronic immune response coincides chronologically with the development of delayed ischemic neurological deficit [24].

Oxygen free radicals or reactive oxygen species (ROS) generated after the immune cell degranulation cause lipid peroxidation (LPO). This oxidative stress contributes to a delayed ischemic injury after SAH [25], since they damage vascular smooth muscle and endothelium, disrupt the blood brain barrier (BBB), produce spasmogens and induct pro-apoptotic enzymes [26,27]. ROS in the subarachnoid space has also been reported to activate protein kinase C (PKC) and Rho kinase, leading to smooth muscle cell constriction [20]. These two enzymes have also been demonstrated to be regulated by nitric oxide (NO•). NO• regulates blood pressure by dilating blood vessels and by inhibiting platelet aggregation and leukocyte adherence to the vascular endothelium [28].

Inflammation and ischemia triggered after SAH activate the synthesis of endothelin-1 (ET-1), a potent vasoconstrictor released by astrocytes and leukocytes [29,30]. ET-1 level is increased at the time cerebral NO• is reduced and this imbalance generates a sustained contraction in cerebral vessels after SAH [31].

As a consequence of the SAH, structural integrity of neuronal and glial cells is compromised. These cells suffer structural damage, leading to a release of specific proteins into the CSF and circulation [32]. Some of these specific proteins are S100B, synthesized in astroglial and Schwann cells; neuron specific enolase (NSE), mainly located in the cytoplasm of neurons; and glial fibrillary acidic protein (GFAP), a monomeric intermediate filament cytoskeleton protein of astrocytes. These protein sera or CSF concentration would be proportional to the cerebral damage degree [32].

Abovementioned metabolites, released into bloodstream or CSF in the pathophysiologic cascade triggered after SAH, have been studied as indicators of neurologic status, CVS development and patient outcome after suffering a SAH, although none of them as been established in clinical practice as SAH patient management tool (Table 1).

2.1. Oxidative stress biomarkers

Oxidative stress is brought on by an oxidant–antioxidant imbalance whereby pro-oxidant production surpasses neutralization capacity, leading to organic damage [33]. The brain is particularly vulnerable to oxidative stress due to its elevated oxygen consumption and high production of reactive radicals [34]. This is augmented by high levels of metal transmission, including iron, which catalyze ROS production. Iron anions are released by the degradation of hemoglobin in the hemorrhagic areas [35]. Many authors have proved that oxidative stress plays an important role in SAH pathogenesis and CVS generation. The principal sources of ROS in a SAH are the superoxide anions from mitochondria due to an ischemic disruption of the electron transport chain, and the various ROS produced from the oxidation of hemoglobin into oxyhemoglobin and methemoglobin [25,36–38].

NO• is a free radical synthesized by nitric oxide synthase (NOS), which has three isoforms: endothelial NOS (eNOS), neuronal NOS (nNOS) and inducible NOS (iNOS) [39,40]. NO• level is directly related with vasospasm generation. It seems that the main enzyme involved in the vasodilatation/vasoconstriction process NO• dependent is the

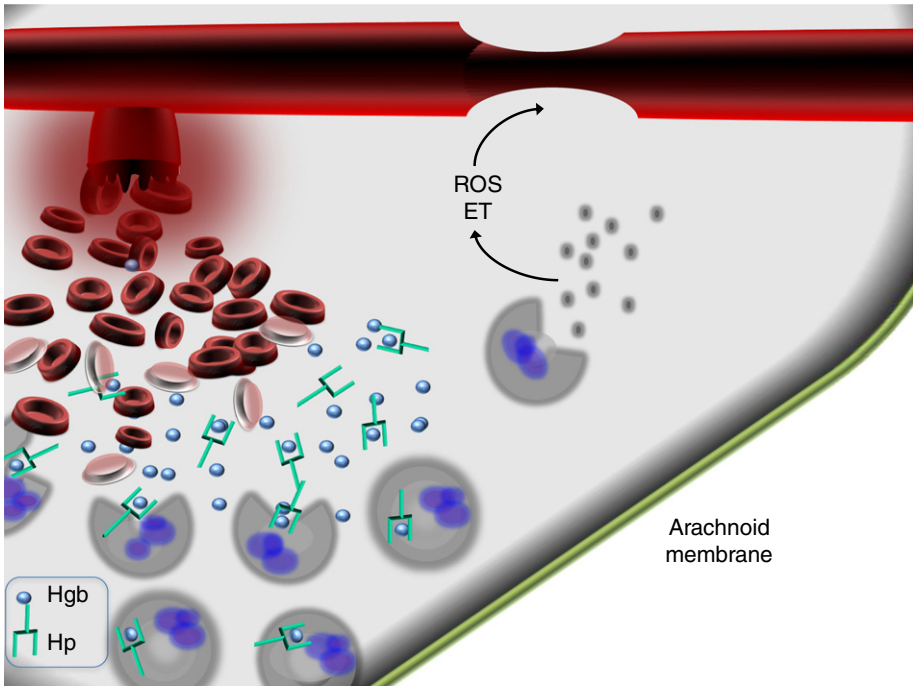

Fig. 1. Pathophysiologic cascade triggered after subarachnoid hemorrhage. Hgb: hemoglobin; Hp: haptoglobin; ROS: reactive oxygen species; ET: endothelins.