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OFFICIAL JOURNAL OF THE WORLD FEDERATION OF NEUROSURGICAL SOCIETIES

WORLD NEUROSURGERY

Vascular

Role of inflammation (leukocyte-endothelial cell interactions) in vasospasm after subarachnoid hemorrhage

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Received 27 September 2008; accepted 27 May 2009

Abstract

Background: Delayed vasospasm is the leading cause of morbidity and mortality after aneurysmal subarachnoid hemorrhage (aSAH). This phenomenon was first described more than 50 years ago, but only recently has the role of inflammation in this condition become better understood.

Methods: The literature was reviewed for studies on delayed vasospasm and inflammation.

Results: There is increasing evidence that inflammation and, more specifically, leukocyte-endothelial cell interactions play a critical role in the pathogenesis of vasospasm after aSAH, as well as in other conditions including meningitis and traumatic brain injury. Although earlier clinical observations and indirect experimental evidence suggested an association between inflammation and chronic vasospasm, recently direct molecular evidence demonstrates the central role of leukocyte-endothelial cell interactions in the development of chronic vasospasm. This evidence shows in both clinical and experimental studies that cell adhesion molecules (CAMs) are up-regulated in the perivasospasm period. Moreover, the use of monoclonal antibodies against these CAMs, as well as drugs that decrease the expression of CAMs, decreases vasospasm in experimental studies. It also appears that certain individuals are genetically predisposed to a severe inflammatory response after aSAH based on their haptoglobin genotype, which in turn predisposes them to develop clinically symptomatic vasospasm.

Conclusion: Based on this evidence, leukocyte-endothelial cell interactions appear to be the root cause of chronic vasospasm. This hypothesis predicts many surprising features of vasospasm and explains apparently unrelated phenomena observed in aSAH patients. Therapies aimed at preventing inflammation may prevent and/or reverse arterial narrowing in patients with aSAH and result in improved outcomes.

Keywords: Endothelial cells; Haptoglobin; Hemoglobin; Inflammation; Leukocytes; Subarachnoid hemorrhage; Vasospasm

Abbreviations: aSAH, aneurysmal subarachnoid hemorrhage; CAM, cell adhesion molecule; CRP, C-reactive protein; CSF, cerebrospinal fluid; E-selectin, endothelial selectin; ELAM-1, endothelial leukocyte adhesion molecule; eNOS, endothelial nitric oxide synthase; ET, endothelin; GMP-140, granule membrane protein-140; Hp, haptoglobin; Hgb, hemoglobin; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; JNK, c-Jun N-terminal kinase; LAM-1, leukocyte adhesion molecule-1; LECAM, leukocyte/endothelial cell adhesion molecule; L-selectin, leukocyte selectin; LFA-1, lymphocyte function-associated antigen-1; LPS, lipopolysaccharide; Mac-1, macrophage antigen-1; MEL, murine erthroleukemia; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; NOS, nitric oxide synthase; NSAID, nonsteroid antiinflammatory drug; PADGEM, platelet activation dependent granule-external membrane; PARP, poly ADP-ribose polymerase; PECAM-1, platelet-endothelial cell adhesion molecule-1; P-selectin, platelet selectin; RBC, red blood cell; TCD, transcranial Doppler; TNFα, tumor necrosis factor-α; TQ, thymocyte-Q; WBC, white blood cell; VCAM-1, vascular cell adhesion molecule-1

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1878-8750/$ - see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.surneu.2009.05.027

1. Introduction

Delayed or chronic vasospasm is the leading cause of morbidity and mortality after aneurysmal subarachnoid hemorrhage (aSAH) [104,105,228,234]. This phenomenon was first documented angiographically by Ecker and Riemenschneider [46] in 1951 and was subsequently correlated to the development of focal neurologic deficits by Fisher and colleagues [63] in 1977. Subsequent to these initial findings in patients with aSAH, cerebral vasospasm has also been observed in other conditions, including meningitis [18,59,177,197,257], traumatic brain injuries [139,140,214,237,265], and after craniotomies [10,51,258]. As a result, there has been an increased interest in understanding the molecular mechanisms responsible for the development of vasospasm.

Vasospasm after aSAH in humans is biphasic, with an acute and a chronic phase [251]. The acute phase typically occurs 3 to 4 hours after the hemorrhage and generally resolves rapidly, whereas the chronic phase typically occurs 3 to 14 days later [251]. This chronic or delayed phase is characterized by the sustained narrowing of the arteries, which can lead to permanent deficits and death in 20% to 40% of patients [76,104,105,228].

The chronic phase of vasospasm can be defined either angiographically or clinically. Angiographic vasospasm is arterial narrowing seen on angiography, whereas clinical vasospasm is the development of focal neurologic deficits presumably as a result of this arterial narrowing. After aSAH, patients can fall into 1 of 3 categories: (1) 33% develop both angiographic vasospasm and clinical signs of ischemia; (2) 43% develop angiographic vasospasm, but no clinical symptoms; and (3) the remaining 24% have neither angiographic nor clinical vasospasm [44]. The ability to predict which patients will develop clinical vasospasm, however, remains limited primarily because the pathophysiology of vasospasm remains unclear.

Inflammation and, more specifically, leukocyte-endothelial cell interactions appear to play a critical role in vasospasm (Table 1) [68]. In this review, we discuss the progress that has been made in understanding the role of inflammation in vasospasm. These advances may have potential implications for prospectively identifying and treating patients at greatest risk of developing chronic vasospasm.

2. Overview of the inflammatory hypothesis of vasospasm after SAH

Hemoglobin (Hgb), which is the iron-containing oxygen-transport protein present within red blood cells (RBCs), is the most abundant protein present in the blood [148]. This protein is extremely toxic when released from RBCs during hemorrhagic and/or hemolytic events, as well as after RBC senescence and breakdown [2,47,72,74,203,211,245]. The immune system prevents this toxicity by efficiently scavenging free Hgb molecules [5]. This is accomplished when macrophages bind to and clear this extracorpuscular Hgb [5]. This binding and clearance, however, relies on the identification of Hgb only when it is conjugated with the haptoglobin (Hp) protein [5]. Haptoglobin is a serum protein that binds to free Hgb with high affinity [5]. Of particular interest is that humans are the only species with 2 forms of haptoglobin (Hp 1 and Hp 2) and that individuals with the Hp 2-2 genotype develop particularly severe inflammatory reactions [70,143,252,253].

During SAH, blood spills into the subarachnoid space. This stimulates the rapid expression of specific cell adhesion molecules (CAMs) on the luminal surface of endothelial cells [68]. This allows macrophages and neutrophils to bind to the endothelial cells and enter the subarachnoid space, where they phagocytose extravasated RBCs and process Hgb via Hp-Hgb complexes [19]. Macrophages and neutrophils, however, remain trapped in the subarachnoid space due to the absence of lymphatics in the central nervous system and impaired cerebrospinal fluid (CSF) flow caused by the SAH [68]. These macrophages and neutrophils then start to die and degranulate 2 to 4 days after their entry into the subarachnoid space [28,41,62,84,160,193]. This results in the release of massive quantities of intracellular endothelins and oxygen free radicals, which results in inflammatory-induced arterial vasoconstriction [28,41,62,84,160,193]. Arterial narrowing, however, is only one manifestation of the inflammatory response to the RBCs in the subarachnoid space. The clinical deterioration of patients "in vasospasm" is because of the extensive inflammatory components leading to meningitis and cerebritis. This explains why other conditions such as bacterial meningitis are also associated with both the meningitic syndrome and arterial narrowing seen after aSAH [18].

3. Hematologic processes

3.1. Hemoglobin, haptoglobin, and the haptoglobin polymorphism in humans

Erythrocytes, or RBCs, are the most common type of blood cell [5]. Red blood cells are continuously produced in the bone marrow at a rate of approximately 2 million cells/s and remain viable for up to 120 days [5]. The major protein component of RBCs is Hgb [180]. Hemoglobin is a complex molecule containing heme groups with iron atoms that temporarily link to oxygen molecules [1]. Intracorpuscular Hgb is usually degraded by macrophages in the reticuloendothelial system, which phagocytoses senescent erythrocytes and degrades Hgb into bile and bilirubin [180]. Bilirubin is less toxic to the body than extracorpuscular Hgb [2,47,72,74,203,211,245].

Extracorpuscular Hgb is extremely toxic but is released into the bloodstream and interstitium during hemolytic and hemorrhagic conditions, respectively [2,47,72,74,203,211,245]. It is a proinflammatory stimulus that up-regulates the expression of endothelial and leukocyte adhesion molecules,