Inflammation and Cerebral Vasospasm After Subarachnoid Hemorrhage

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Aneurysmal subarachnoid hemorrhage (aSAH) remains a leading cause of morbidity and mortality in patients who survive the initial ictus, primarily as a result of the development of delayed or chronic vasospasm.[1–4] Vasospasm after aSAH in humans is a biphasic phenomenon[5] in which an acute phase that typically occurs 3 to 4 hours after an aSAH and generally resolves rapidly, is followed by a chronic phase that occurs 3 to 14 days later.[5] This chronic or delayed phase is characterized by sustained arterial narrowing that can lead to permanent deficits and death in 20% to 40% of patients.[1–3,6] Cerebral vasospasm has also been observed in other conditions, including traumatic brain injury,[7–15] after craniotomies,[16–18] and in meningitis.[19–23] Interactions between leukocytes and endothelial cells are fundamental factors in the inflammatory response to injury, and seem to be critical components in the pathophysiology of posthemorrhagic cerebral vasospasm.[24] This review summarizes the growing body of evidence that supports the prominent role of inflammation in this condition, and discusses its potential implications in the development of diagnostic and therapeutic strategies for this condition.

THE INFLAMMATORY HYPOTHESIS OF VASOSPASM AFTER SUBARACHNOID HEMORRHAGE

During SAH, blood deposition into the subarachnoid space results in release of free hemoglobin (Hgb), which is extremely toxic.[25] To counteract free Hgb toxicity, the immune system stimulates rapid expression of specific cell adhesion molecules (CAMs) on the luminal surface of the endothelial cells.[24] This allows macrophages and neutrophils to bind to the endothelial cells and enter the subarachnoid space, where they phagocytose extravasated red blood cells (RBCs) and remove free Hgb. The binding and clearance of extracorpuscular Hgb relies on the identification of Hgb only when it is conjugated with haptoglobin (Hp),[25] a serum protein that binds to free Hgb with high affinity.[25]

After RBC phagocytosis and Hgb clearance, however, macrophages and neutrophils remain trapped in the subarachnoid space because of the absence of lymphatics in the central nervous system (CNS) and impaired cerebrospinal fluid (CSF) flow caused by the SAH,[24] and within 2 to

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4 days after their entry into the subarachnoid space, macrophages and neutrophils die and degranulate.[26–31] This results in a release of intracellular endothelins (ET) and oxygen-free radicals into the interstitial and subarachnoid spaces that ultimately cause an inflammation-induced arteriopathy and arterial vasoconstriction.[26,28–32] Arterial narrowing, however, is only 1 manifestation of the inflammatory response that follows SAH; the clinical deterioration of patients with arterial narrowing by imaging or ultrasonography is the result of a more complex and robust inflammatory response that results in meningitis and cerebritis. This hypothesis explains why the meningitic syndrome and arterial spasm seen after aSAH, which results in delayed ischemic deficits and stroke, is also present in other pathophysiologic entities such as bacterial meningitis and traumatic brain injury (TBI), among others.[19] This hypothesis is illustrated in **Fig. 1**.

HEMATOLOGICAL COMPONENTS OF VASOSPASM

Hgb and Hp

Hgb is the iron-carrying oxygen transport metalloprotein that constitutes most of the structure of the RBCs. Although intracorpuscular Hgb is usually degraded by macrophages in the reticuloendothelial system, extracorpuscular Hgb is a proinflammatory molecule[33] that requires complex interactions for proper recycling. Free Hgb also

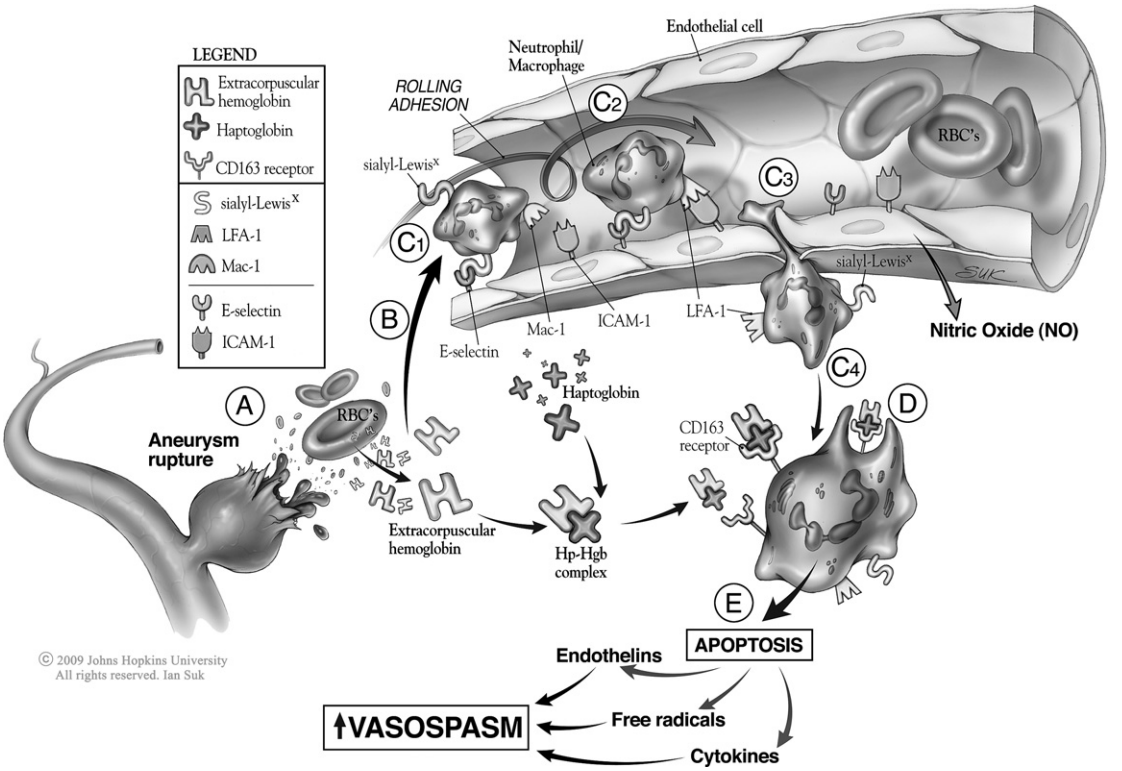

Fig. 1. Cascade of events resulting in posthemorrhagic cerebral vasospasm. (A) Rupture of a cerebral aneurysm results in subarachnoid hemorrhage. (B) Extravasated RBCs are lysed and release Hgb into the subarachnoid space that induces upregulation of CAMs on leukocytes and endothelial cells. (C1) Circulating granulocytes and neutrophils transiently bind with selectins on endothelial cells (E-selectins) through their sialyl-Lewis moieties and roll along the intraluminal surface. (C2) Leukocyte rolling is arrested by tethering to the endothelial surface through strong bonds between leukocyte integrins (LFA-1 and Mac-1) and endothelial immunoglobulin superfamily proteins (ICAM1). (C3) Transendothelial leukocyte migration into the subarachnoid space occurs. (C4) Intrathecal leukocytes migrate toward senescent RBCs and phagocytose free Hgb molecules. (D) Extracorpuscular Hgb binds to Hp and forms an Hp-Hgb complex. The CD163 scavenger receptor on the macrophage surface binds with variable affinity to the Hp-Hgb complex depending on the Hp genotype (weaker in Hp 2-2 genotypes than in Hp 1-1) and internalizes it for phagocytosis, thereby degrading Hgb into bilirubin. (E) Trapped intrathecal leukocytes undergo apoptosis within days, and release ET, free radicals, and proinflammatory cytokines, which in turn enhance leukocyte migration, decrease NO-mediated vasodilation, and result in delayed chronic cerebral vasospasm. (*Courtesy of* Johns Hopkins University, Baltimore, MD.)

reduces vasodilation induced by nitric oxide (NO), and the synergistic proinflammatory and vasospastic effects of extravascular Hgb seem to be critical in the development of vasospasm.[27,30]

Hepatocytes synthesize large quantities of Hp in serum.[34] This protein couples with Hb through a stable, high affinity bond[35–38] and ameliorates the toxicity of free extracorpuscular Hgb. Although in humans the Hp gene has 2 alleles, designated Hp 1 and Hp 2, other mammalian species have only a single Hp1 allele.[39–41] The dimeric protein coded by Hp 1-1 more efficiently binds and promotes the clearance of Hgb molecules when compared with the cyclical Hp 2-2 protein,[42] and seems to have superior antiinflammatory, immunomodulatory, antioxidant, and vasodilatory effects in vitro and in animal studies.[42–46] Hp 2-2, however, provides protection against some infectious disease, a characteristic that has promoted its dissemination in the human gene pool.

The Inflammatory Response

Inflammation constitutes a biphasic response with an acute and a chronic period. Although the acute period constitutes a short event that occurs immediately after the initial injury and uses polymorphonuclear neutrophils, macrophages, and monocytes as its primary effector cells,[47,48] the chronic period occurs in a delayed manner in days or weeks, and has lymphocytes and plasma cells as the main effector cells.[49,50] Acute inflammation results from the combination of a vascular response that includes arteriolar relaxation (increasing blood flow) and local endothelial cell contraction (increasing vascular permeability)[47,48] and a cellular response that involves neutrophils, macrophages, and monocytes, which migrate to the inflamed site and phagocytose the particles that stimulated the inflammatory response. These inflammatory effector cells eventually degranulate, and release enzymes and other toxic intermediates into the extravascular space that precede and subsequently promote chronic inflammation.[51] Continuous proinflammatory stimulation primarily mediated by lymphocytes and monocytes/macrophages that invade the affected tissue and release cytokines (eg, interferon-γ), reactive oxygen species, and hydrolytic enzymes result in chronic inflammation.[49,50] This chronic component develops in days or weeks, and can persist for many months or years.[49,50]

INFLAMMATION AND CHRONIC VASOSPASM

Although Ecker and Riemenschneider[52] first described angiographic cerebral vasospasm in 6 patients with aSAH in 1951, William Gull[53] had already reported a case consistent with vasospasm in England in 1859. Cerebral arterial vasospasm was experimentally recreated in laboratory models in the early twentieth century,[54–57] and the clinicopathologic correlation of cerebral infarction in the presence of a patent cerebral vasculature was provided by Robertson[56] in 1949, who studied a series of patients with ruptured aneurysms and concomitant cerebral infarction, and hypothesized that the infarctions resulted from transient spasm of the supplying arteries and not from mechanical compression from the aneurysms. The first correlation of angiographic vasospasm and focal neurologic deficits, however, was not reported until Fisher and colleagues' study in 1977.[58] Despite increasing clinical and experimental evidence, the pathophysiology of vasospasm continues to be elusive and modest therapeutic progress has been made to date.

Clinical Correlates of Inflammation and Vasospasm

Hyperthermia

Hyperthermia or fever was the first clinical sign that indicated a subjacent inflammatory response in these patients,[59] and its appearance correlated with the onset of chronic vasospasm.[60] These observations were later confirmed by Weir and colleagues,[61] who found that of all patients with aSAH who developed clinical vasospasm, 60% had a temperature greater than 37.5°C in the 6 days before vasospasm onset, which represented nearly twice the incidence of patients with lower temperatures. These findings were replicated in other studies that also correlated persistent fever after aSAH with less favorable outcomes.[62]

Leukocytosis

Increased white blood cell (WBC) counts have been shown to correlate with an increased risk of clinically significant vasospasm and worst outcomes.[61,63–67] Although the impact of leukocytosis on clinical outcomes was first reported in 1974 by Neil-Dwyer and Cruikshank,[65] a link between increased WBCs and vasospasm was not confirmed until 1987, when Spallone and colleagues[67] correlated leukocytosis with the development of ischemia after aSAH. Detailed chronologic correlation between leukocytosis and the time course of chronic vasospasm was later provided by Niikawa and colleagues,[66] and an independent association between peak leukocyte counts and the development of cerebral vasospasm was then reported in a multivariate analysis by McGirt and colleagues.[64]

Serologic markers of inflammation in vasospasm

Immune complexes are seen in patients with post-hemorrhagic vasospasm,[68–70] along with activated complement cascade proteins,[68,71] and C-reactive protein (CRP).[72] In fact, Rothoerl and colleagues[72] have shown that CRP is significantly increased in patients who developed symptomatic vasospasm and that it correlates with the worst neurologic outcomes.

Histopathologic changes in vasospastic cerebral vessels

Evidence of a significant inflammatory arteriopathy has been described on histopathologic examination of cerebral arteries from patients with clinical and angiographic vasospasm and is consistently replicated in multiple experimental models of the disease.[73–77] For instance, increased endothelial penetration of monocytes within arteries in proximity to ruptured-aneurysm sites,[73] macrophage invasion of the tunica media and adventitia of vessels in angiographic vasospasm,[75] and positive immunofluorescence for IgM and C3 in the endothelium of spastic arteries in patients with aSAH[74,76] have been reported.

Experimental Evidence of Inflammation in Vasospasm

Induction of vasospasm with proinflammatory agents

A clear pathophysiologic link between inflammation and cerebral vasospasm has been difficult to demonstrate despite numerous clinical studies that correlated a robust inflammatory response with the progression of vasospasm.[60–67,69,70,78] To elucidate the nature and causality of this relationship, researchers have replicated arterial vasospasm in the absence of blood products and other conditions associated with SAH by administering several proinflammatory agents in experimental models.[79–83] Vasospasm has been successfully induced by injected latex and dextran beads into the cistern magna of dogs,[81] administration of polystyrene latex beads[83] and talc (crystallized hydrous magnesium sulfate),[79,80] and locally delivered lipopolysaccharide (LPS) into the subarachnoid space of rabbits.[82] Controlled release of LPS in particular resulted in chronic vasospasm in a dose-dependent fashion, which replicated the basilar artery vasospasm induced by SAH in the same model.[82] These studies demonstrated that significant arterial vasospasm could be induced despite the absence of RBCs or Hgb in the subarachnoid space and provide further confirmation of the role of inflammation in the development of chronic vasospasm.

Prevention of vasospasm with immunosuppressive or antiinflammatory agents

Immunosuppressive or antiinflammatory agents have been postulated as potential treatments for chronic cerebral vasospasm in various animal models[84–92] and in a few human clinical trials[93–97] with varied results. Among the proposed agents, corticosteroids,[84–86,93,94] cyclosporine,[81,87,95–97] tacrolimus (FK-506),[88–90] and nonsteroidal antiinflammatory drugs (NSAIDs)[85–92] have been most extensively studied.

Corticosteroids are steroidal hormones with antiinflammatory and immunosuppressive properties[98] that primarily affect lymphocyte proliferation and function, and tend to suppress chronic rather than acute inflammation.[99] Experimental administration of high dose methylprednisolone decreased cerebral vasospasm, ameliorated arterial wall abnormalities, and suppressed prostaglandin E2 synthesis in animal models.[84–96] Human clinical studies by Chyatte and colleagues[93] in 21 patients at high risk for vasospasm by clinical criteria showed that methylprednisolone therapy improved neurologic outcomes, decreased mortality, and reduced delayed cerebral ischemia. A multicenter study by Hashi and colleagues[94] then followed that included 52 centers with 140 enrolled patients and evaluated the effects of hydrocortisone administration after vasospasm onset. Results showed improved mental status, speech, and motor function in hydrocortisone treated patients 1 month after treatment.

Cyclosporine causes T-cell dysfunction by inhibiting interleukin-2 (IL-2) transcription,[100] and its use in animal models of experimental SAH has produced conflicting results.[91,95,101] Clinical studies with cyclosporine have also had mixed results. Although in a study by Manno and colleagues[95] cyclosporine failed to prevent chronic vasospasm in patients with Fisher grade 3 SAH, a study by Ryba and colleagues[76,97] showed that a combination of cyclosporine with nimodipine significantly improved outcomes in patients who underwent early clipping (<72 hours) after a SAH.

In addition to their antipyretic and analgesic effects, NSAIDs also have potent antiinflammatory properties, mediated in part by a nonselective inhibition of cyclooxygenase expression, which reduces prostaglandin synthesis.[102] Furthermore, certain NSAIDs such as ibuprofen have been shown to prevent leukocyte migration into the periadventitial space[103–105] by inhibition of endothelial intercellular adhesion molecule 1 (ICAM1; CD54) expression. White and colleagues[92] have also

shown that intravenous NSAID administration in a canine model of SAH significantly reduced the severity of vasospasm. In this study, however, NSAIDs were injected 30 minutes before and 3 hours after induction of SAH, and despite their positive findings these time points would limit therapeutic replication in human trials.[92]

Decreased levels of activated complement proteins in serum have been shown to ameliorate cerebral vasospasm in experimental models[83,106,107] and in human subjects.[108,109] Nafamostat mesilate is a serine protease inhibitor that prevents complement activation and experimentally reduced angiographic vasospasm in rabbits with hemorrhagic[109] and latex bead-induced vasospasm.[83] These findings were replicated in a small clinical trial in which Nafamostat reduced the incidence of vasospasm alone[109] and in combination with a thromboxane synthetase inhibitor.[108]

Current Molecular Evidence of Inflammation in Vasospasm

CAMs and leukocyte migration

The development of monoclonal antibodies led to the discovery of cell-adhesion molecules (CAMs), which facilitated a detailed understanding of leukocyte-endothelial cell interactions during inflammation. The 3 classes of CAMs that regulate leukocyte-endothelial cell interactions are selectins, integrins, and immunoglobulin superfamily proteins. Identification of the location and variable expression of CAMs elucidated and clarified the complex process that results in leukocyte adhesion, diapedesis, and migration, which is now known to involve 3 primary steps: selectin-facilitated rolling, chemokine-induced activation, and integrin-dependent arrest.[51] The initial tethering of leukocytes to the vessel walls results from the interaction between sialylated carbohydrates on the leukocyte membrane and endothelial selectins.[110] This interaction is followed by binding of leukocyte receptors to chemoattractants released from the injured tissue and integrin activation.[111] Integrins in turn bind to immunoglobulin superfamily members expressed on the endothelium, which increases leukocyte adhesiveness and causes rolling leukocytes to arrest.[112] Arrested leukocytes then diapedese and migrate to sites of inflammation.[113]

Selectins

Selectin expression facilitates the formation of adhesions between leukocytes and endothelial cells and reflects an evolving inflammatory response.[114,115] E-selectin has been found to be elevated in SAH patients, with higher concentrations seen in patients who develop moderate or severe vasospasm.[116] Although P-selectin levels appeared to be higher in patients with low-grade SAH who developed ischemia, L-selectins were higher in patients who did not develop delayed cerebral ischemia.[117,118] Selectin inhibition in a mouse model of SAH resulted in improved lumen patency and decreased peripheral WBC counts when compared with SAH controls.[119]

Integrins

The main integrins involved in leukocyte adhesion and migration are LFA-1 and Mac-1.[120,121] The authors have analyzed the effects of systemically administered anti-LFA-1 and Mac-1 monoclonal antibodies on morphometric arterial vasospasm in rats,[122] rabbits,[123] and monkeys after experimental SAH[124] and found a significant decrease in posthemorrhagic vasospasm in all models, which correlated with fewer periadventitial infiltration of neutrophils and macrophages.[122] Intracisternal monoclonal antibody administration in a rabbit model by Bavbek and colleagues[125] produced similar results.

Statins are 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors clinically used as cholesterol-reducing agents. Their ability to reduce the expression of proinflammatory cytokines and inhibit leukocyte integrins confers them potent antiinflammatory activity also.[126,127] In a randomized controlled trial by Tseng and colleagues,[128] patients with aSAH (n = 80) were randomized to receive either oral pravastatin or placebo within 72 hours of their initial hemorrhage. Patients treated with pravastatin had a 32% reduction in vasospasm incidence, vasospasm-related neurologic deficits decreased by 83%, and mortality decreased by 75% when compared with patients treated with placebo.[128] A subsequent study by the same group found that pravastatin also improved neurologic outcomes at 6 months.[129] In addition, a case-control series by Parra and colleagues[130] showed decreased incidences of clinical vasospasm and improved 14-day functional outcomes in patients receiving statins before developing aSAH compared with patients who did not use statins. Kramer and colleagues and McGirt and colleagues,[131,132] however, in recent retrospective studies did not find significant differences in the severity of angiographic or clinical vasospasm, or in the neurologic outcomes of patients receiving statins after aSAH.

Immunoglobulin superfamily proteins

Immunoglobulin superfamily proteins, such as ICAM1, have been found to be upregulated in patients who develop clinical vasospasm[116] and increased expression correlates with poor

neurologic outcomes following aSAH.[133–135] The authors have shown that anti-ICAM1 monoclonal antibodies can decrease the extent of femoral artery vasospasm and inhibit periadventitial infiltration of macrophages and neutrophils in a rat model.[136] This antibody produced a similar effect in basilar artery vasospasm and inflammatory cell infiltration as an anti-LFA-1 monoclonal antibody in animal models.[122]

The use of drugs like statins and ibuprofen, which downregulate immunoglobulin superfamily expression, also decreases vasospasm in experimental studies. Several clinical studies have shown that statins decrease serum ICAM1 levels in hypercholesterolemic patients,[126,127,137–139] and may contribute to the beneficial effects of statins in reducing the incidence of vasospasm in clinical trials.[128–131,140] Ibuprofen is another antiinflammatory with anti-ICAM1 and antivascular cell adhesion molecule 1 (VCAM1) activity.[103,141] Local sustained delivery of ibuprofen via controlled-release polymers significantly inhibited femoral artery vasospasm and decreased the number of periadventitial monocytes and macrophages when administered at 0 and 6 hours after hemorrhage in a rat model.[105] These results were replicated in rabbit[142] and monkey SAH models.[104] Chyatte and colleagues[85] also demonstrated that ibuprofen prevented ultrastructural changes in the cerebral vessel walls of dogs after blood injection. Clinical use of ibuprofen, however, is limited because its efficacy at preventing vasospasm has been shown only if it is administered within 6 hours of hemorrhage.[104,105,142]

The critical role of leukocytes and inflammation in the pathophysiology of chronic vasospasm is widely supported by the experimental findings described earlier and by the efficacy of monoclonal antibodies against integrins and immunoglobulin superfamily CAMs in animal models. In the rabbit and primate SAH models, treatment with monoclonal antibodies against CAMs prevents leukocyte migration and vasospasm despite the presence of RBCs and Hgb in the subarachnoid space, which shows that chronic vasospasm does not occur in the absence of leukocytes or attenuated inflammation.

Other proinflammatory proteins

Cytokines and other proinflammatory proteins such as c-Jun N-terminal kinase (JNK) and poly (ADP-ribose) polymerase (PARP) have also been implicated in vasospasm. The main proinflammatory cytokines that have been shown to be elevated in patients with vasospasm include IL-1, IL-6, IL-8, and tumor necrosis factor α.[143–149] Administration of drugs that inhibit cytokine production has resulted in attenuation of vasospasm in animal models.[150,151] JNK is a mitogen-activated kinase involved in the inflammatory response.[152] The use of a JNK inhibitor has been found to decrease angiographic vasospasm, improve neurologic function, reduce leukocyte infiltration, and decrease IL-6 production following blood injection in a canine model.[153] PARP is a nuclear enzyme that regulates CAM expression and neutrophil recruitment during inflammation.[154] In a rabbit model of SAH Satoh and colleagues[155] showed that PARP activation occurred in the smooth muscles and adventitia of blood-exposed vessels, and that a PARP inhibitor decreased the severity of vasospasm.

NO Depletion and ET Elevation

Endothelium-derived relaxing factor or NO is synthesized in the blood vessel wall in response to shear stress or metabolic dysfunction, and results in significant arterial vasodilation.[156] After hemorrhage, however, free Hgb disrupts several components of NO-mediated vasodilation. Besides inflammation, NO dysfunction is believed to play a contributory role in the development of posthemorrhagic vasospasm and has been a target in several experimental studies.[156] Following aSAH, CSF levels of nitrites, a major source of endogenous NO,[157,158] have been found to be significantly decreased in patients who develop vasospasm.[159,160] The authors have shown that intrathecal NO supplementation via controlled-released polymers prevented vasospasm in rat and rabbit models of SAH,[161,162] and that delayed polymer implantation 24 or 48 hours after SAH also ameliorated vasospasm.[162] Several studies have also shown that selective intracerebral NO injection,[163] intraventricular NO injection,[164] and systemic nitrite infusions improved the severity or decreased the incidence of vasospasm experimental and clinical studies.[160]

ET are powerful vasoconstrictors commonly expressed by vascular endothelial cells.[165,166] Although several studies have documented significant intrathecal ET-1 level increases in aSAH patients that develop vasospasm,[167,168] others have not.[169] Anti-ET-1 monoclonal antibodies,[170] anti-ET receptors antibodies,[171,172] and ET activation enzyme inhibitors[173] have been shown to decrease vasospasm in some,[171,172] but not all studies[174]; therefore, additional studies are needed to clarify its role in the pathophysiology of chronic vasospasm.

NONHEMORRHAGIC VASOSPASM

Cerebral vasospasm seems to develop in other pathologic conditions that affect the CNS in the absence of aSAH, such as TBI,[9,10,15] infectious meningitis,[19–23] and after craniotomies.[16–18] Inflammation also seems to contribute significantly to the development of vasospasm in these other conditions.

Reported incidences of vasospasm in patients after TBI have ranged from 25% to 40%,[9] regardless of intracranial penetration.[10,175] The incidence[176] and the pathophysiology[15,175] of post-TBI vasospasm closely resemble those of posthemorrhagic vasospasm. Post-TBI vasospasm is also biphasic; it has an acute and a chronic period,[15] and its time course parallels posthemorrhagic vasospasm.[175] Despite the limited experimental and clinical studies on post-TBI, these observations suggest that trauma or trauma-related hemorrhage triggers a perivascular inflammatory response that results in cerebral vasospasm.

In addition to posttraumatic vasospasm, it has been reported that vasospasm can develop in patients who have undergone craniotomies for nonvascular causes.[16–18] Bejjani and colleagues[16] reported a case of a 6-year-old girl who underwent a craniotomy for an intracranial schwannoma who later developed angiographically confirmed vasospasm. El Hendawy and colleagues[17] reported 14 cases of vasospasm following craniotomies for intraaxial and extraaxial brain tumors, including gliomas and meningiomas. As with posttraumatic vasospasm, it is believed that the same mechanisms underlying post-aSAH vasospasm may explain postcraniotomy vasospasm.

Several cases of meningitis-associated cerebral vasospasm have been reported.[19–23] The authors have shown that meningitis-associated vasospasm follows a time course similar to aSAH-associated vasospasm,[19] and that its pathophysiology could also be explained by the inflammatory hypothesis. Following bacterial meningeal colonization and infection, endothelial activation signaling is triggered, leukocyte infiltration into the subarachnoid space occurs, and cytokines and other proinflammatory agents are released,[177–182] which upregulate CAM expression,[179–183] and enhance the inflammatory response that results in cerebral vasospasm.[179–183]

FUTURE DIRECTIONS

Despite numerous studies with promising experimental therapies for aSAH-induced vasospasm,[184–186] hypertensive-hypervolemic-hemodilutional (“triple H”) therapy[187] still remains as the mainstay of clinical vasospasm treatment. Large prospective controlled trials, however, have failed to show that prophylactic triple H therapy significantly reduces the incidence of clinical or angiographic vasospasm or that it improves neurologic outcomes.[184–188] Additional treatments including transluminal balloon angioplasty,[189,190] lumbar drainage of CSF,[191,192] and intracisternal thrombolysis[193] have been used as salvage therapies but they typically result in minimal benefits and increased complications. Pharmacologic therapies involving systemic calcium channel blockers (nimodipine),[185,194] a nonglucocorticoid free radical scavenger (tirilazad mesilate),[195,196] and intraarterial[197,198] have suffered from these same limitations. Arterial narrowing was prevented effectively by nicardipine[199] and clazosentan[200] in clinical trials, but neurologic outcomes remained unchanged.

Limited progress has been made in the development of techniques to identify prospectively aSAH patients at risk for chronic cerebral vasospasm that would enable early and selective application of targeted therapies to prevent or ameliorate the inflammatory response and restore NO-mediated vasodilation. Among the potential molecular markers for predicting which patients will develop clinical vasospasm following aSAH, the Hp genotype has gained recent interest.[201] Of all aSAH patients, 30% develop symptomatic vasospasm, 50% develop asymptomatic angiographic vasospasm, and 20% do not show signs of angiographic or clinical vasospasm. This distribution follows the prevalence of Hp genotypes in humans,[202] and the Hp 2-2 genotype in particular seems to be present in 30% of humans, which correlates with the incidence of clinical vasospasm in aSAH patients. The authors have genetically engineered mice to express the Hp 2-2 genotype,[39–41] and showed that Hp 2-2 mice developed more severe morphometric and clinical vasospasm after experimental SAH than wild-type Hp 1-1 mice.[201] Vasospasm in these animals correlated with increased periadventitial neutrophils and macrophages, which strongly suggests a relationship between the Hp 2-2 genotype, inflammation, and cerebral vasospasm.[201] Further studies are needed to clarify the relationship between the Hp genotype and inflammation, and only prospective clinical studies will define the effect of an Hp genotype in the development of chronic cerebral vasospasm.

Based on the substantial evidence on the contribution of inflammation to the pathophysiology of vasospasm presented, a hypothesis that links the various pathophysiologic events described in this review and elsewhere in the literature with the

development of chronic vasospasm has been formulated: after aSAH, erythrocyte extravasation into the subarachnoid space induces endothelial upregulation of CAMs, primarily of ICAM1, which can also be upregulated by bacterial meningitis and traumatic SAH. ICAM1 upregulation enables endothelial cells to bind to LFA-1 or Mac-1 proteins on the leukocyte surface and mediate transendothelial leukocyte migration into the peri-adventitial space. Once in the subarachnoid space, extravasated leukocytes phagocytose subarachnoid erythrocytes in SAH or bacteria in bacterial meningitis. The absence of a lymphatic intrathecal system prevents leukocyte recirculation and trapped leukocytes die and degranulate in the subarachnoid space 2 to 4 days after the triggering event, which corresponds to the onset and time course of chronic vasospasm in humans. Leukocyte degranulation results in ET and oxygen free radicals release, and NO dysfunction. Although these molecular mechanisms are strongly amplified in Hp 2-2, they are moderately present in Hp 2-1 patients and lead to clinical vasospasm in Hp 2-2 patients, angiographic vasospasm in Hp 2-1 patients, and do not result in vasospasm in Hp 1-1 patients. Validation of this hypothesis will require extensive future testing in experimental models and clinical settings.

SUMMARY

Delayed or chronic cerebral vasospasm results in major morbidity and mortality for patients after aSAH. Despite extensive clinical and experimental analysis of this phenomenon its pathophysiology remains poorly understood and the biologic and genetic principles behind the variability in the development of clinical vasospasm have not been elucidated. The cumulative evidence presented strongly supports the role that inflammation and leukocyte-endothelial cell interactions play in the pathophysiology of vasospasm, but translation of these findings into clinically effective therapies will require further molecular and genetic understanding of this inflammatory arteriopathy.

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