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Original Investigation

Connecting the Early Brain Injury of Aneurysmal Subarachnoid Hemorrhage to Clinical Practice

Anevrizmal Subaraknoid Kanamada Erken Beyin Hasarının Klinik Pratik ile İlişkilendirilmesi

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ABSTRACT

Aneurysmal subarachnoid hemorrhage (SAH) is a devastating neurological disease that has a mortality rate as high as 67% in some series. Traditional research and treatment has focused on addressing the delayed events of cerebral vasospasm following SAH. However, the physiological and cellular events of early brain injury (EBI) make significant contributions to patient outcomes and may even be a more significant factor than delayed cerebral vasospasm. EBI is the result of physiological derangements such as increased intracranial pressure (ICP), decreased cerebral blood flow (CBF), and global cerebral ischemia, which results in blood brain barrier dysfunction, inflammation, and oxidative cascades that lead to neuronal cell death. The consequence of these events to the patient is often death or significant neurological disability. The link between EBI and outcome has come under intense focus with recent studies failing to show improved outcomes following significant inhibition of cerebral vasospasm, and research into the inhibition of EBI cascades is being perused as an effective means of treating SAH patients.

KEYWORDS: Subarachnoid hemorrhage, Early brain injury, Edema, Apoptosis, Infarction, Oxidative stress, Inflammation

ÖZ

Anevrizmal subaraknoid kanama (SAH) yıkıcı bir nörolojik hastalık olup kimi serilerde %67 ye varan yüksek mortalite oranına sahiptir. Geleneksel araştırma ve tedavi, SAH sonrası serebral vazospazmın gecikmiş olaylarına odaklanmıştır. Ancak, erken beyin hasarının (EBI) fizyolojik ve hücresel olayları hastaların prognozunda önemli katkıya sahiptir ve gecikmiş vazospazmdan daha önemli bir faktör olabilir. EBI; artmış intrakraniyal basınç (ICP) ve azalmış beyin kan akımı (CBF) gibi fizyolojik dengesizliklerin bir sonucudur. Oluşan global beyin iskemisi, kan-beyin bariyeri disfonksiyonu, inflamatuar ve oksidatif kaskadlar nihayetinde nörönal hücre ölümü ile sonuçlanır. Neticede bu olaylar hastanın sıklıkla ölümüne ya da ciddi nörolojik disabilitesine neden olmaktadır. Serebral vazospasmın ciddi inhibisyonuna rağmen iyileşmiş sonuçların elde edilememesi, EBI ile prognoz arasındaki bağlantıya yoğun bir odaklanmaya neden olmuştur ve EBI kaskadlarının inhibisyonu araştırılmalarının SAH'lı hastaların tedavisindeki anlamı dikkatle değerlendirilmektedir.

ANAHTAR SÖZCÜKLER: Subaraknoid kanama, Akut beyin hasarı, Ödem, Apoptozis, Infarktüs, Oksidatif stres, Enflamasyon

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INTRODUCTION

Aneurysmal subarachnoid hemorrhage (SAH) accounts for up to 7% of all stokes (15, 74) and carries a mortality rate as high as 67% (28,69). Advances in the surgical and intensive care treatment for SAH patients over the last several decades have reduced the previous mortality rates by as much as 15% (28). However, many of these advances do not address the progression of the disease at a molecular level, which begins in the moments immediately following rupture of the aneurysm. The pathophysiology that immediately follows aneurysm rupture has been recognized as the greatest contributor to mortality after SAH for over a decade, and 12-15% of the patients with a ruptured aneurysms die before reaching medical care as a result of these events (6, 69). Early Brain Injury (EBI), is a term that refers to the whole brain injury that occurs in the 24 to 72 hours following SAH (8, 40, 61). While basic science efforts have traditionally focused on the delayed events of vasospasm following SAH, typically occurring 3-14 days after rupture (11, 37, 48), EBI refers to the events that occur, or are at least initiated, in the brain before the development of vasospasm.

EBI is a multifaceted event with complex pathways that often have overlapping outcomes; several different pathways may contribute to neuronal apoptosis, or blood brain barrier (BBB) breakdown (Figure 1). Neuroscience subspecialties (neurovascular, neuro-immunological, etc) each tend to focus on specific aspects of the molecular mechanisms of EBI, but ultimately therapy will probably consist of combination of treatments that address the many aspects of the injury. Failure to focus earlier clinical and research efforts on the treatment of EBI may have been because the opportunity for intervention was either felt to have already passed by the time the patient reached the hospital, or the pathophysiology was simply deemed untreatable. Studies are contributing to a mounting body of evidence that EBI, whose cascades are set into motion immediately following aneurysm rupture, not only contribute to the initial signs and symptoms of SAH, but also contribute to the delayed neurological deterioration traditionally attributed to vasospasm, as well as long term functional outcome (3, 13, 60, 63, 64, 75). Recent studies, such as the CONSCIOUS-1 clinical trial of clazosentan, have also shown that the reversal of vasospasm itself fails to improve outcome, suggesting that events outside vascular contraction contribute to delayed neurological decline as well as poor long term outcome in SAH. In CONSCIOUS-1, the endothelin-1 receptor antagonist clazosentan demonstrated a 65% reduction in angiographic vasospasm that resulted in only mild reductions in delayed neurological deficits, and failed to result in improved functional outcome (47, 80).

This review illustrates the pathophysiology of early brain injury, reviews some of its molecular mechanisms, and provides evidence to suggest that the patients who have survived long enough to reach neurosurgical intensive care are candidates for interventions that aim to halt the molecular cascades of early brain injury that may continue for days following the inciting event.

Consequences of Increased Intracranial Pressure and Cerebral Edema following SAH

Perhaps the most immediate event following the rupture of an intracranial aneurysm is the acute rise in intracranial pressure (ICP) that at least initially results from the mass effect of the introduction of blood into the subarachnoid space (57, 82). Additional mechanisms contributing initial increased ICP also include impeded CSF drainage (12, 17, 81), cerebrovascular dysfunction resulting in vascular engorgement (24), and the formation of acute cerebral edema (65, 70, 71). When an aneurysm ruptures, the ICP rises to levels approximating diastolic blood pressure within minutes. It then falls over several minutes to reach a much lower baseline, but remains at higher than normal pressure (23, 58). The fall in ICP following its initial spike results from compensatory mechanisms related to the Monro-Kellie hypothesis: as extravascular blood enters the subarachnoid space, intracranial CSF is displaced into the spinal cord and/or forced into the venous system, additionally venous and then arterial blood volume is displaced from the intracranial space (42, 43, 55). If these compensatory mechanisms are not enough to support critical levels of brain perfusion the patient may expire. Even though the patient may survive the initial hemorrhage the new steady state with elevated ICPs is correlated with poor outcome (27). Current therapies for elevated ICP following SAH include the placement of intraventricular, and even lumbar cistern drainage systems (56, 78). These traditional means of lowering the ICP are effective,

but there are still instances of poorly controlled ICP despite these measures. Additional benefit may be gained from therapies aimed at reducing the acute development of cerebral edema (9, 76). The incidence of cerebral edema following SAH has typically been overlooked, as most clinicians focus on the development of hydrocephalus or the evacuation of large subarachnoid clots which are more obvious reasons for elevated ICP (Figure 2A,B). Studies on the incidence of global cerebral edema following SAH have found an incidence of roughly 8% (9, 34, 38, 41). The clinical relevance of cerebral edema in SAH has been highlighted by cases reporting the need for decompressive craniectomy following its development (71), as well as animal studies demonstrating the presence of global cerebral edema within minutes to hours of aneurysm rupture (7, 32, 73, 76). Additionally, Claassen et al found that 40% of patients with global cerebral edema on CT had a 40% mortality at 3 months, compared to only an 18% mortality for patients without global cerebral edema (9), and Kreiter et al. found cerebral edema to be one of the major predictors of cognitive dysfunction, mortality and morbidity following SAH even after factors such as age, aneurysm size, and neurological grade at admission were considered (38).

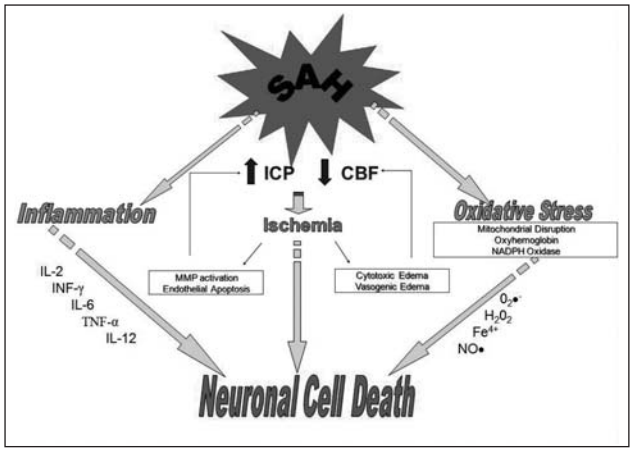

Figure 1: *Inter-relationships of Early Brain Injury Pathways. Physiological disturbances such as increase ICP and decreased CBF, inflammation, and oxidative stress culminated in neuronal cell death.*

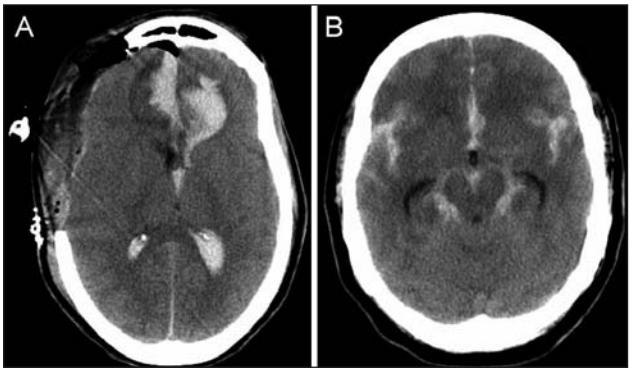

Figure 2: *Variables Responsible for Increased ICP following Aneurysmal SAH.* ***A)*** *In a case illustrating some of the more recognized causes of refractory ICP in SAH patients, a 46-year-old female presented with Hunt Hess Grade 5 SAH. The aneurysm was clipped under emergent circumstances due to elevated ICP despite ventricular drainage and a decompressive craniectomy and partial evacuation of the frontal intracerebral hematoma was performed at the time of clipping (as shown above).* ***B)*** *A second patient with refractory ICP. This patient underwent coiling of an anterior communicating artery aneurysm, and despite ventricular and lumbar cistern drainage developed refractory ICPs. The scan above shows subarachnoid blood and diffuse cerebral edema. This case illustrates an instance were specific therapies against EBI may counteract the development of edema, help control ICP, and improve patient outcomes.*

Pathways to Global Cerebral Edema Following SAH

The mass effect of subarachnoid blood, and the development of hydrocephalus are examples of mechanical causes for increased intracranial pressure, however, the development of global cerebral edema is a processes that occurs at the cellular level. A major consequence of the initial ICP spike following aneurysm rupture is the development of global cerebral ischemia resulting from the circulatory arrest that occurs as intracranial pressure (ICP) transiently reaches levels approximating arterial pressures; this is phenomenon is clinically correlated to the loss of consciousness following SAH (57, 58). This hypoxic state results in energy failure in neurons and glia and initiates the cascade of events leading to cytotoxic edema (61). Ischemia also results in apoptosis in the cells that constitute he blood brain barrier (BBB) (36). Endothelial cells and perivascular astrocyte cell death leads to the diffusion of serum from the vascular lumen into cerebral tissues (vasogenic edema). Numerous intracellular second messenger cascades have been implicated in initiating the apoptotic signal that disrupts the BBB (8, 62, 83). Park et al. demonstrated apoptosis in cerebral endothelial cells and an increased BBB permeability after experimental SAH that was reversed with caspase inhibition (62). Additionally, vascular

endothelial growth factor (VEGF), a mitogen involved in angiogenesis and vascular permeability (53, 84, 85), is elevated following SAH, and initiates cell death pathways in the neurovascular unit that comprised the BBB (40, 83). In addition, matrix metalloproteinases (MMPs), which degrade the type IV collagen that makes up the basement membrane of the BBB, are known to be increased following experimental and human SAH, and contribute to BBB breakdown (29, 54, 66-68, 72). The development of therapies that target these enzymes may have clinical efficacy as Yatsushige et al. found that decreased MMP-9 activity was associated with a preserved basement membrane and reduced cerebral edema 24 hours after experimental SAH in rats (83). The development of therapies to reduce BBB disruption is complicated by the fact that the therapeutic window for these treatments may be limited. Already evidence exists that inhibiting factors acutely may prove beneficial, but if the inhibition is prolonged it may prove detrimental to recovery, as in the case of VEGF (85) and MMPs (49).

Concurrent Mechanisms of Brain Injury: Oxidative Stress and Inflammation

SAH introduces free radical and inflammatory cell mediated brain injury through the free radical inducing properties of extravascular hemoglobin and cytokine secretion from leukocytes and erythrocytes.

Many studies have provided evidence that oxidative stress plays a significant role in EBI. An imbalance favoring the production of reactive oxygen species (ROS) versus their neutralization by intrinsic antioxidant systems has been demonstrated in the brain following SAH in both experimental models and humans (19, 35, 50, 51). The foremost source of free radicals following SAH are the leakage of superoxide anions from mitochondria due to an ischemic disruption of the electron transfer chain, and the cascade of free radicals produced from the auto-oxidation of hemoglobin (1, 50). The liberation of oxyhemoglobin (oxyHb) into the CSF following SAH is a major producer of (02•) and hydrogen peroxide (H202) as it undergoes auto-oxidation to methemeglobin (2). Methemoglobin and oxyhemoglobin will also react with hydrogen peroxide to generate ferrylhemoglobins (Fe4+), another strong oxidizing agent (22). In the brain there are several enzymatic protective systems that are in place against free radical production, and during normal cellular respiration, superoxide dismutases (SODs), glutathione peroxidases (GSH-Px), and catalase are the significant enzymatic scavengers in brain tissue (46). However, following SAH these enzymatic systems become downregulated or modulated in a way that reduces their antioxidant capabilities (18, 19, 46, 50).

Through their highly reactive unpaired electrons, free radicals are directly damaging to the neurovascular unit (endothelial cells, pericytes, astrocytes) and neurons through the promotion of lipid peroxidation, protein breakdown, and DNA damage (61). The consequences of these events are neuronal apoptosis, endothelial injury, and blood brain barrier (BBB) breakdown. Figueroa et al demonstrated that oxidative stress induced cortical neuron death through the mitochondrial pathway of apoptosis as well as through necrosis (16). Endo et al., through the use of transgenic rats, showed that reducing oxidative stress during acute brain injury reduced apoptosis, and promoted increased survival and neurological function in experimental SAH (13). The administration of systemic antioxidants in experimental SAH has also proven to reduce oxidative stress, protect the BBB, and improve neurological scores (21, 31, 79). Free radical mediated damage is non-specific and affects many cell types. The advantage of direct free radical scavenging, or the up regulation of native protective systems during acute injury, is the ability to prevent the initiation of multiple damaging cascades. However, utilizing an effective therapeutic window may be the biggest challenge. It is possible that by the time a patient is available to receive treatment the damage caused by free radicals may have already been completed, and may explain the poor performance of free radical scavengers in clinical trials (25, 33, 44, 45).

Several ingestions have characterized the infiltration of lymphocytes and macrophages into the CNS following subarachnoid hemorrhage, indicating that SAH may elicit its own characteristic inflammatory reaction (39, 52). The CNS has several intrinsic mechanisms that provide a somewhat immunologically privileged site; part of this immune suppression appears to involve the inhibition of neurotrophils, which do not appear to be a significant part of the inflammatory response following SAH (59, 77). Debate exists as to whether

or not the infiltration of lymphocytes into the CNS is neuroprotective, or detrimental to recovery. Conflicting reports are highly debated (26). Investigators have sought to resolve the conflicting evidence by investigating the subpopulations of T cells following various CNS injuries, particularly distinguishing between type 1 (Th1), type 2 (Th2) and type 3 (Th3) T helper cell subsets through the identification of their characteristic cytokines. Investigations in ischemic stroke models demonstrate the potential for the development of a Th1 cellular response, resembling CNS autoimmune disease, that results from the exposure of CNS antigens to the immune system that are usually protected from recognition by an intact BBB (4, 5). The development of immune tolerance to CNS antigens prior to experimental stroke has been found to reduce Th1 autoimmunity, reduced infarct size, and improve outcomes (5). Additionally, eliciting a Th2/Th3 response, characterized by the secretion of immunomodulatory cytokines (IL-4, IL-10, transforming growth factor ß1 (TGF- ß1), promotes the immunological tolerance of CNS antigens and may augment neuroregeneration (20, 26). These findings have lead to the experimental application of drugs known to illicit Th2 immune responses for the treatment of stoke and other CNS diseases (20, 26). The concept of immunomodulation may prove to be beneficial while avoiding the pitfalls blanket immunosuppression (14).

A Common Final Pathway: Cell Death and Brain Infarction

Ischemia, cerebral edema, oxidative stress, and inflammatory reaction all make themselves clinically relevant through their involvement in neuronal cell death, which is ultimately responsible for the dysfunction that follows SAH (Figure 1). Neuronal cell death has been quantified following experimental SAH during the early brain injury period (60, 64, 75), and the degree of neuronal cell death has been linked to the physiological events of aneurysm rupture, such as the degree of initial cerebral blood flow reduction (64). The most obvious indication of cell death, albeit from apoptosis or necrosis, is the development of an infarction, and its appearance following SAH has been well documented (38, 63, 70). Infarction not only occurs following severe vasospasm (65), but is also the result of the physiological changes surrounding the initial bleed (70), and its presence under these circumstances is a clear indicator for poor outcome (38). Evidence from several studies also demonstrates significant long-term neurological disability following SAH without the occurrence cerebral vasospasm (10, 30, 38).

Studies have shown that the acute administration of neuroprotectants, such as nimodipine, reduces the incidence of infarction whether it is from early brain injury or cerebral vasospasm (63). Many more opportunities for intervention exist as more about the apoptotic cascades initiated in SAH are revealed. Yatsushige et al. (83) demonstrated the programmed cell death of neurons mediated through the activation of a JNK/cJun pathway, while Cahill et al (8) demonstrated that the activation of the three classical apoptotic pathways following SAH results in the loss of cortical and hippocampal neurons 72h after SAH. Each of these studies demonstrated that the inhibition of apoptotic pathways not only reduced cellular death, but also resulted in a significant improvement in functional outcome.

CONCLUSIONS

SAH continues to be a devastating neurological disease but recent studies are continuing to shed light on the importance of EBI and its relevance to patient survival and long-term functional outcome. Cerebral vasospasm and its clinical consequences should no longer be recognized as the only treatable cause of poor outcome following SAH.

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