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Pathophysiology of Brain Somatic Interactions in Aneurysmal Subarachnoid Hemorrhage - Review and Update

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Abstract

This commentary summarizes and updates current evidence regarding pathophysiologic mechanisms of brain somatic interactions in aneurysmal subarachnoid hemorrhage. It discusses primary and secondary injurious processes after aneurysmal rupture. It reviews current state of knowledge of multi-organ involvement in this disease condition, including brain-cardiopulmonary, neuroendocrine and renal manifestations. Emerging evidence is also summarized regarding brain-gastrointestinal, immune and hematologic systems.

Primary and Secondary Injury Spectrum

Patients with ruptured brain aneurysms have a mortality rate of at least 45% in the first month after rupture. Neurological damage can be from primary injury of the aneurysm rupture and from a number of secondary injurious processes. Increased intracranial pressure from aneurysmal rupture results in decreased cerebral blood flow. Deranged autoregulation occurs with blood-brain barrier disruption, further worsening increased osmotic pressures and cerebral edema. Secondary injurious processes include:

1. peri-lesional and cortical spreading ischemia,
2. reperfusion injury,
3. microcirculatory thrombi and spasm,
4. imbalance between oxygen supply and demand,
5. anaerobic metabolism with lactic acidosis,
6. neuronal membrane dysfunction and release of excitatory neurotransmitters,
7. harmful products, including reactive oxygen species, calcium influx, oxyhemoglobin leading to increased endothelin-1, and deoxyhemoglobin leading to decreased nitric oxide, and
8. cell-mediated apoptosis.

Pathophysiologic Mechanisms of Brain Somatic Interactions in Aneurysmal Subarachnoid Hemorrhage

In patients with ruptured brain aneurysms, excessive activation of the sympathetic nervous system and systemic inflammatory response can lead to deleterious effects on the internal mechanisms of multiple organ systems. Anatomically, components of the central autonomic nervous system which are excessively activated after brain aneurysm rupture include the insular cortex, amygdale, hypothalamus, parabrachial complex, nucleus of the tractus solitaries and ventrolateral medulla. Overstimulation of the insular cortex and amygdale can trigger seizures and cardiac arrthymias. Patients with posterior circulation aneurysms are especially prone to altered internal regulatory mechanisms. Blood around the lower brainstem can stimulate the dorsal and solitary tract nuclei of the medulla. Excessive activation of hypothalamic nuclei can lead to altered consciousness, as well as activation of neuronal networks for cardiac, cardiovagal, vasomotor and respiratory neurons via the preganglionic sympathetic neurons of the lateral horns (interomediolateral cell column) of the upper thoracic segments of the spinal cord.

Excessive activation of the sympathetic nervous system leads to surge of catecholamine release. This catecholamine surge then acts on postganglionic fibers to the heart and blood vessels. In turn, autonomic control over blood pressure regulation and vascular resistance is lost. Disrupted blood brain barrier is the end result as fluid and proteins leak into worsening areas of brain edema. Pathologically, the cardiac ventricle is stunned. This can manifest as altered cardiac rate and rhythm, as well as troponin elevation. Cardiac stunning refers to cardiac beta receptor hyperactivation and hypercontraction where contraction band necrosis can result. An extreme case of this is the observation of stunned apical and mid ventricular segments in Takotsubo cardiomyopathy. Electrocardiographic, troponin and echocardiographic evidence correlate with plasma measurement of brain natriuretic peptide, a protein release from the cardiac ventricle with peak values on post rupture day 1. The brain site of brain natriuretic peptide production does not seem to be as affected as cerebrospinal fluid levels of brain natriuretic peptide are not elevated. Further physiologic evidence from pulse contour analysis points to global decrease in cardiac ejection function, with subsequent moderate increases in extravascular lung water index by day 3 post rupture. This is consistent with increased catecholamines in peripheral arterioles which can increase pulmonary venous pressures and enhance pulmonary vascular permeability. The combination of increased pulmonary vascular pressure, increased pulmonary vascular permeability, decreased cardiac contractility and increased volume from resuscitation can lead to hydrostatic pulmonary edema where hydrostatic pressures favouring edema formation overwhelm the opposing oncotic pressures.

As a result of the apparent increased preload, the cardiac atrium is stretched. Plasma atrial natriuretic peptide levels peak at day 2 after

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aneurysmal rupture. Cerebrospinal fluid levels of atrial natriuretic peptide remain normal, suggesting that the primary source of atrial natriuretic peptide is the cardiac atrium. Together, both atrial and brain natriuretic peptides then act on renal tubules triggering sodium and volume loss. Without appropriate resuscitation, plasma sodium levels can fall drastically by day 4 post rupture. Judicious therapy is essential to maintain sodium and water balance, as natriuretic states often herald the onset or worsening of clinical vasospasm. The renin-angiotensin-aldosterone system is activated in a delayed manner between days 4 and 6 post aneurysmal rupture. It is activated as a compensatory mechanism for sodium and water loss. In addition to altered renin-angiotensin-aldosterone system, those with renal disorders may suffer from negative consequences of: (1) metabolic disorders (including altered sodium levels), and (2) blood clotting defects (including excessive activation of fibrinolytic states due to systemic inflammation, as well as dysfunction platelets in those with uremic states). This can predispose the affected patients to cerebral edema and further bleeding, especially in cases with disrupted cerebral autoregulation.

Other Brain-Body Interactions

Current evidence also provides pathophysiologic mechanisms on the following brain-body interactions:

- Fevers markedly increase cerebral metabolic rate and can worsen secondary injurious processes in the brain. Early onset fevers can be secondary to dysfunction of temperature regulation centers in the hypothalamus. Late onset fevers are more likely to be infectious, but can include fevers secondary to drugs and pulmonary embolism. Those with fevers are more prone to seizures.
- Original insights are also emerging to delineate the significance of neuro-gut axis in influencing neurologic outcome. Epidemiologic data point to development of cerebral edema in those with hepatic disease. Possible pathophysiologic mechanisms include: (1) altered blood flow to the brain, (2) release of chemicals which are toxic to the nervous system, (3) altered blood clotting cascade, and (4) overall systemic inflammatory states. Aneurysmal rupture can predispose these patients to decompensated states with acute increases in cerebral blood flow (luxuriant perfusion) and decreased differences in the oxygen content between arterial and venous blood. The end result is a viscous cycle of cerebral hyperemia and cerebral edema, along with neuronal swelling and death.

In addition, genetic polymorphism evidence links endothelial nitric oxide (eNOS) VTNR a allele to increased clinical risk of delayed ischemic neurologic deficits after aneurysmal subarachnoid hemorrhage. As there exists upregulation of inflammatory, immune and apoptotic mechanisms with aneurysmal rupture, there exist therapeutic roles of milrinone, as this compound mediates vasodilation through both cAMP and anti-inflammatory mediated increases in nitric oxide concentrations [1-5].

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