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New Perspectives in Aneurysmal Subarachnoid Hemorrhage

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INTRODUCTION

A subarachnoid hemorrhage **(SAH)** is defined by the presence of blood in the subarachnoid space and the most frequent etiology is trauma. Spontaneous SAH is mostly secondary to the rupture of aneurysmal malformations in about 80% of cases and it represents 3% of all strokes [1] (Figure 1). Other causes are represented by arterio-venous malformation rupture, vasculitides involving the central nervous system, cerebral vessels dissection, tumors, venous thrombosis and drug abuse. In about 15% of cases the source of bleeding is not identified.

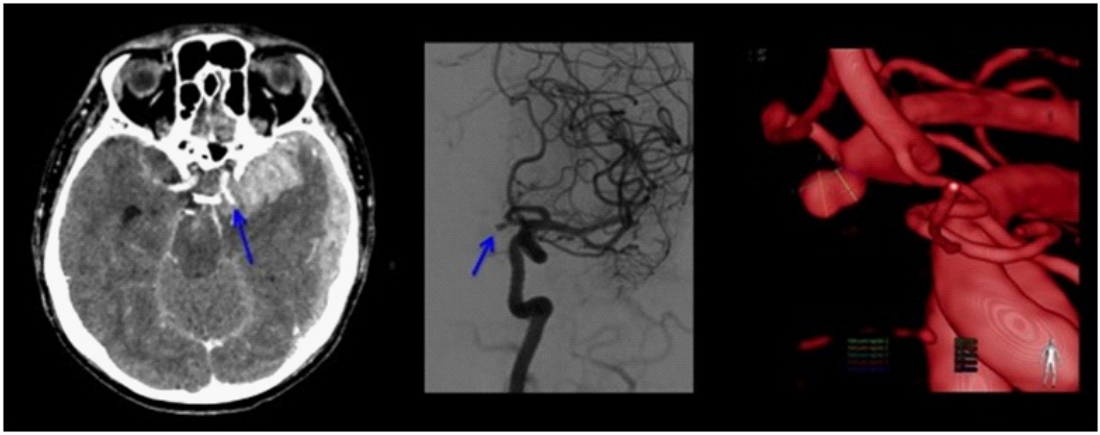

Figure 1: Cerebral CT scan showing a SAH Fisher IV with a left-temporal hematoma at the temporal pole and as associated subdural component. An aneurysm of the posterior communicating artery was detected at the sequences with contrast administration (Figure 1A). The patient arrived with a GCS 3/15 and a left fixed mydriasis. A surgical clipping was immediately performed and the patient actually presents a modified Rankin Scale at 3.

The figure 1B and 1C show another case of a ruptured aneurysm of the anterior communicating artery (arteriography with catheterization of the right internal carotid artery and 3D reconstruction respectively). The aneurysm was clipped and the patient had a favorable evolution.

The incidence of SAH is about 9per 100,000 person-year [2], with a higher rate in Japan and Finland and it has not changed during the last decades.

About 10% of patients die in the pre-hospital setting, while another 10% die during the first days after the hemorrhage. The overall mortality is thus high, ranging from one to two thirds of patients according to the study considered [3,4]. A slight fall in mortality has been observed during the last decades [5] probably reflectingthe refinement in endovascular techniques and in microsurgical interventions, the improvement in the timing of interventions as well as progresses in the neurocritical care area.

However the long-term functional prognosis remains deceiving and, as half the patients are younger than 55 years (about 20% of cases occur between 15 and 45 years [6]), SAH has a high social and economic impact.

More than one third of patients will in fact remain dependent in their daily activities at 5 years after the hemorrhage. This may be due to a functional impairment, cognitive decline as well as behavioral changes modifying social interactions.

Many factors may complicate the in-hospital stay of these patients, such as an early aneurysmal rebleeding in the acute phase, the development of cerebral ischemia and oedema, hydrocephalus, seizures ormedical complications.

Nowadays the clinical practice is based on the early treatment of the source of bleeding (through surgery or endovascular procedures) and on an intensive neurocritical care management. The prevention and control of cerebral vasospasm is actually considered the mainstay of treatment to limit delayed complications. However clinical and preclinical studies conducted to limit the incidence and severity of vasospasm showed only a marginal improvement in functional outcomes. Furthermore the radiological improvement of cerebral vasospasm seems not to correlate with an improved prognosis [7,8].

Recently many studies tried to identify the mechanisms contributing to the early and delayed brain injury in the setting of SAH and thus the real determinants of the poor prognosis. Their understanding might in fact improve the clinical outcome of SAH patients.

The aim of this chapter is to explore these new fields of research through an update of the literature on the argument.

EARLY BRAIN INJURY

The term "early brain injury" **(EBI)** was used for the first time in 2004 to define the acute events occurring within 72 hours from the primary hemorrhage and leading to the activation of a pathological cascade. SAH is in fact generally characterized by a systemic and intracranial response more severe than other types of stroke [9] (Figure 2).

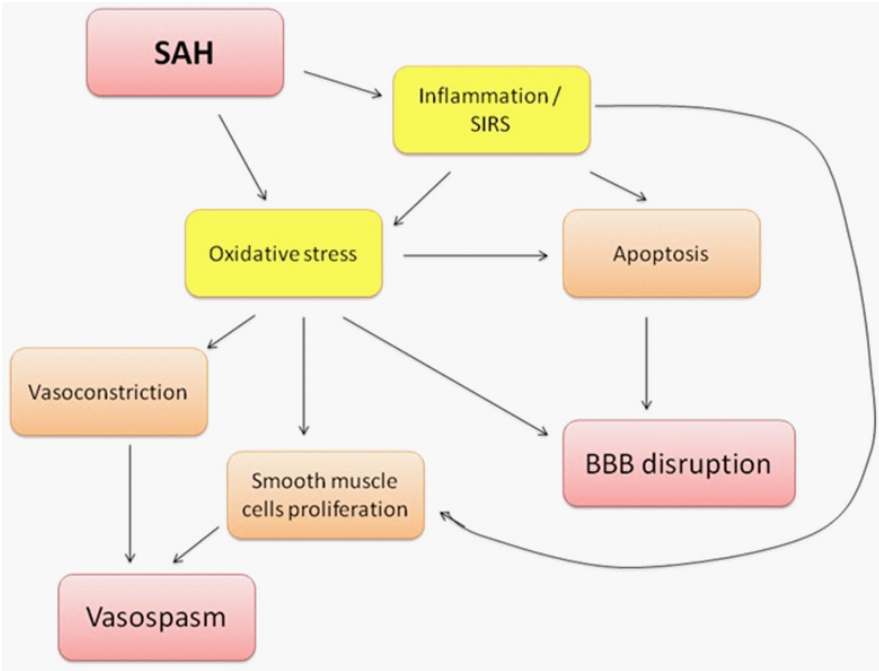

Figure 2: The multiple factors contributing to the early brain injury after SAH are here resumed. The consequences are the activation of apoptotic pathways, the BBB disruption and vasospasm of proximal vessels as well as microcirculation disruption.

Activation of the Inflammatory Response

The presence of blood in the subarachnoid space provokes a huge activation of the systemic inflammatory response **(SIRS)**, with a release of cytokines in the bloodstream. It was shown that febrile patients have a worse prognosis than apyretic patients and the aggressive treatment of fever aiming at normothermia is considered reasonable in the acute phase of SAH [10].

Blood inflammatory parameters seem also to be correlated with the prognosis and the risk of development of cerebral vasospasm [11] and recently IL-6 was proposed as tool to monitor the clinical progression [12].

A correlation between the level of inflammatory parameters and prognosis might thus be possible.

Oxidative Stress

A huge oxidative stress accompanies SAH. Hemoglobin and blood degradation products may act as free radicals or trigger the inflammatory cascade though the activation of the NF-kB pathway.

The free radicals, as well as some inflammatory mediators may cause a multifactorial activation of the apoptotic process. All these factors lead to a disruption of the integrity of the blood brain barrier **(BBB)**, thus modifying the homeostasis of the central nervous system and predisposing to the formation of vasogenic and cytotoxic edema.

Cerebral Autoregulation Disruption

The acute disruption of cerebral autoregulation after SAH is secondary to the acute suffering of endothelial and smooth muscle cells, with hyperemia and concomitant ischemia in other cerebral areas. The arterioles lose in fact their capability to modulate the resistances in accordance with the flow and a general activation of the coagulation cascade strongly modifies the physiological cerebral blood flow.

Neuroendocrine Deregulation and Electrolytic Unbalances

Electrolytic unbalances may contribute to EBI development. Between 10% and 30% of patients with SAH develop hyponatremia because of a cerebral salt wasting syndrome or inappropriate secretion of the antidiuretic hormone. These patients seem to be at risk of developing delayed neurological deficits 3 times more than normonatriemic patients [13]. Because of a diffuse ischemic suffering of the cerebral parenchyma, the intracellular levels of calcium increase thus provoking a vasospasm because of a hypercontractility of the smooth muscle cells, a synaptic dysfunction and an activation of the apoptotic process. Also the low levels of serum magnesium typical of patients with SAH may contribute to this intracellular hypercalcemia through the activation of NMDA receptors [14].

Nitric Oxide – Endothelin-1 Unbalance

An alteration in the balance between the nitric oxide **(NO)** and the endothelin-1 **(ET-1)** may also be a factor contributing to EBI and then later to vasospasm development [15,16]. A delayed increase in NO level after 24h from the hemorrhage was associated with a poor prognosis [17], probably because of its action as free radical. Also the levels of ET-1 are increased in the early period after SAH [18], thus mediating vasoconstriction and hyperplasia of the vascular wall after a prolonged stimulation [19].

Increased Sympathetic Drive

SAH seem to be responsible for hypothalamic changes with an increase in the sympathetic drive determining an augmentation of the serum levels of catecholamines that may be responsible for numerous cardio-pulmonary complications. Patients developing such systemic complications may have a higher risk of delayed cerebral ischemia and poor prognosis [20].

DELAYED BRAIN INJURY AND VASOSPASM

The term "delayed brain injury" is used to designate the pathological events occurring after 72hours from the primary bleeding and leading to delayed cerebral ischemia **(DCI)**. DCI is considered an important factor impacting on the global prognosis of patients with SAH as about 30% of patients surviving to the primary bleeding died later or has a poor prognosis because of DCI [21]. DCI is defined as any neurological deterioration secondary to cerebral ischemia, persisting form more than 1 hour and not attributable to another cause. The high-risk period is between 4 and 10 days after the primary hemorrhage.

For about a century cerebral vasospasm has been considered as the single most important factor predictive of delayed ischemia and death after the efficient treatment of ruptured aneurysms [22]. However, after the deceiving results deriving from the treatment of vasospasm alone, recent evidences start to hypothesize those new factors might determine the development of delayed ischemic neurological deficit.

The mechanisms belonging to EBI have surely an impact on DCI development and the question is if we can modify this process with precocious interventions.

Cerebral Vasospasm

Cerebral vasospasm has classically been considered the major determinant for ischemia and clinical deterioration (symptomatic vasospasm). In the acute phase it is determined by a hyper contractility of smooth muscle cells, while in the chronic phase it is determined by a hyperplasia of the muscular layer, probably mediated by the activation of the inflammatory cascade and oxidative stress [23]. Normally it begins the third day after SAH, lasting 2 or 3 weeks and with a peak at 6-8 days.

Microcirculation Spasms and Thrombosis

Aside the vasospasm of cerebral proximal vessels evident at the angiogram, SAH is accompanied by a substantial modification of the microcirculation with spasms and lacking of auto regulation. A hypoper fusion of the territory supplied by these vessels is thus possible. Furthermore SAH favor the activation of the coagulation cascade and thus the formation of thrombi in the microcirculation. This process may modify the vascular plasticity of the cerebrum, blocking the possibility of a collateral revascularization and causing a "no-reflow" phenomenon. Some indirect ways to quantify the residual auto regulation in SAH patients have been used, such as the ORx, correlating the cerebral perfusion pressure with the partial pressure of brain tissue oxygen. According to these studies an analysis of the residual auto regulation capacity may help in defining which patient will develop a DCI [24].

Cortical Spreading Depolarization and Necrosis

The neuronal sufferings due to the presence of SAH translate into an alteration of the trans-membranous potential with a long-lasting depolarization. This abnormal wave may cause neuronal edema and dendritic distortion and in front of a mismatch between metabolic needs and supply, the neuronal death may occur as common final pathway [25].

Hydrocephalus

Acute hydrocephalus, developing during the first days after SAH, was described in about 20% of patients. It may be obstructive if the hemorrhage impairs the correct circulation of the CSF or malresorptive (more frequent in the sub acute and chronic phase). It may cause clinical deterioration but the realization of a head CT and the insertion of an EVD may quickly relieve the situation. If not correctly treated it may represent a negative prognostic factor and predispose to the development of DCI.

Seizures

To establish the real incidence of seizures in SAH patients is difficult. Risk factors for developing seizures are: the presence of a middle cerebral artery aneurysm, an intraparenchymal hematoma and a poor clinical status at hospital admission. The administration of a prophylactic treatment is not indicated and phenito in should be avoided because it was associated with a higher rate of medical complications [10]. A continuous EEG may help in detecting subclinical or non-convulsive status, above all in unconscious patients.

CLINICAL MANAGEMENT

The hospitalization of SAH patients in a high-volume center provided of a neuro-intensive care unit and a precocious diagnosis of DCI are crucial elements in the management of SAH patients. This is obtained through the combination of serial neurological evaluation and imaging. Cerebral CT or MRI is normally scheduled every 48 hours for poor-grade patients and an additional neuromonitoring is generally used during the risk period for DCI. This monitoring may include trancranial doppler, ICP, CPP, brain tissue oxygenation and microdialysis. TCD may easily

detect cerebral vasospasm in proximal cerebral arteries but it is strictly linked to the operator's experience and patient's cranial window. The role of ICP monitoring in SAH patients is actually questioned as most of the evidences come from patients with severe head injury. Early elevation of ICP values is easily explicable by the presence of additional blood in the intracranial compartment (Monro-Kellie law) and the extent of ICP elevation has for long been used to predict outcome after SAH. However the correlation between ICP value and long-term functional outcome is debated [26].

Brain tissue oxygenation and microdialysis values may detect hypoxic and ischemic suffering in a precocious manner but the tissue sampling is limited and the localization of the probes should be optimal to have informative data. A multimodal monitoring might however represent a useful tool to guide therapeutic decision and in predicting prognosis.

A continuous EEG may also help in checking patients with a poor neurological status.

THERAPEUTIC OPTIONS

The discovery that other factors, different from cerebral vasospasm, may influence the functional outcome of aSAH patients and has steeply increased the range of investigation for new therapeutic strategies.

An overview of the different therapeutic options to treat patients with aSAH is reported in Figure 3.

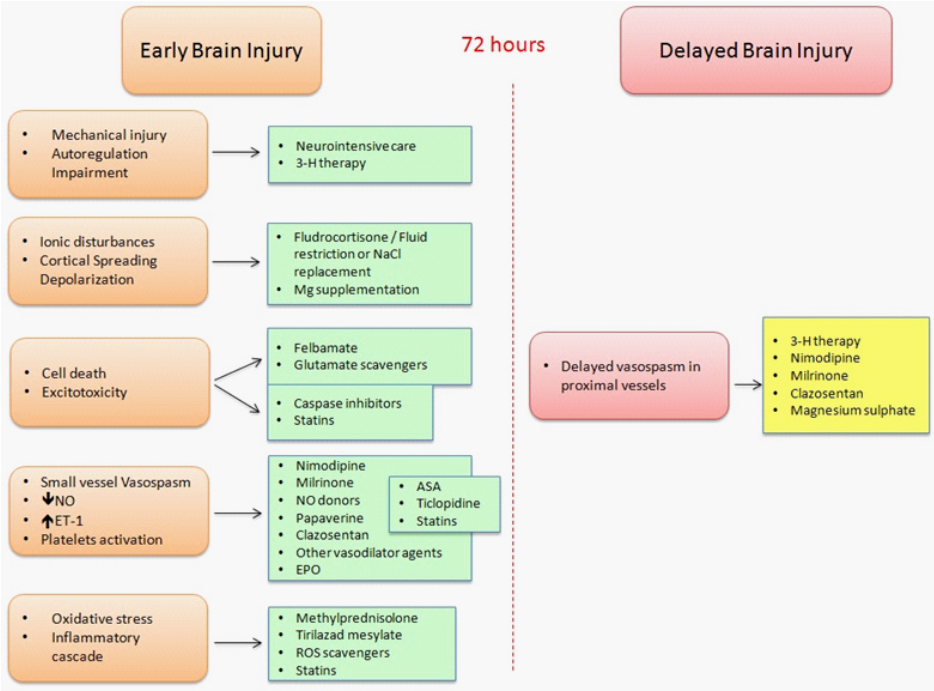

Figure 3: The different clinical and experimental therapeutic strategies are here summarized.

Classically the triple-H therapy (hypertension, hypervolemia and hemodilution) and calcium channel blockers are the mainstay of treatment to prevent the development of DCI. However during the last decades the utility of aggressive hemodilution and hypervolemia has been questioned, in favor of moderate hypertension and euvolemia,to limit the incidence of cardiopulmonary complications [27,28]. Fludrocortisone may also be administered to limit an excessive diuresis and natriuresis.

Calcium channel blockers block specifically dihydropyridine-type calcium channels, thus diminishing the intracellular levels of calcium in the smooth muscle cells and decreasing the risk of cerebral vasospasm [29]. However calcium-antagonists showed neuro-protective properties even independently from their effects on vasospasm and they may thus have beneficial effects aside the angiographic response. The supplementation in magnesium sulphate is supposed to act in the same direction: magnesium is in fact an antagonist of calcium channels (e.g. NMDA-receptor) and at it may reduce the activation of inflammatory pathways. However multiples studies failed to show a beneficial effect of magnesium on vasospasm [30].

ET-1 antagonists (Clazosentan) showed deceiving results on clinical trials. The functional outcomes and death were in fact not influenced even in front of an improvement of cerebral vasospasm [7]. Other vasodilator agents have been investigated with controverting results, such as milrinone, 17-beta estradiol and nitric oxide donors.

Angioplasty and direct infusion of vasodilator drugs in cerebral arteries are alternative solutions used in cases of severe vasospasm, because of the risks associated to this invasive procedure [31].

The use of antioxidants showed promising results in preclinical models [32] but clinical trials are lacking. The utility of non-steroidal and steroidal anti-inflammatory agents to reduce the burden of inflammation is still under investigation [33,34]. Statins are hydroxymethyglutaryl-**(HMG-)** CoA reductase inhibitors: they may have an anti-inflammatory effect and induce the expression of eNOS thus increasing NO production. Encouraging results were found in patients treated with statins after aSAH [35] but the debate on their cinical application in the setting of SAH is still open.

CONCLUSION

The prognosis of patients with SAH depends on multiple factors and the role of vasospasm has probably been overestimated. Inflammation, oxidative stress and disregulation of the microcirculation with the formation of spasms and thrombi might early determine the natural evolution of the pathology. Therapeutic options to treat EBI and then contributors to DBI may thus represent a future solution to improve the tragic prognosis of these patients.

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