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Glial cell response after aneurysmal subarachnoid hemorrhage — Functional consequences and clinical implications☆

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ABSTRACT

Glial cells, both astrocytes and microglia, respond to neurodegenerative processes and to brain damage by a process called reactive gliosis. This response is highly context dependent, varies from mild to severe, and can be protective or detrimental for neural functioning. In patients with a subarachnoid hemorrhage from a ruptured aneurysm, the acute glial response is important to restrict the initial damage. Patients who survive the hemorrhage and early brain injury, often suffer from delayed cerebral ischemia or persisting cognitive impairment. Glia emerge as versatile cells that can modulate synapses and can control the microcirculatory blood flow in the brain. Therefore, a sustained activation of glial cells can affect normal brain functioning. Here we review the current literature on the glial response induced by aneurysmal subarachnoid hemorrhage in humans and in animal models. We discuss how reactive gliosis can affect brain functioning and how it may contribute to early brain injury, delayed cerebral ischemia and cognitive impairment after aneurysmal subarachnoid hemorrhage. This article is part of a Special Issue entitled: Neuro Inflammation edited by Helga E. de Vries and Markus Schwaninger.

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1. Introduction

Subarachnoid hemorrhage (SAH) from a ruptured aneurysm is a subtype of stroke that occurs in relatively young patients (median age around 55 years of age) and has high rates of case fatality and morbidity [137]. The most important determinants of poor functional outcome after aneurysmal SAH are early brain injury (EBI) in the first 72 h after the SAH, rebleeding of the aneurysm, and delayed cerebral ischemia (DCI) 4 to 14 days after ictus. Many survivors, even those with good functional outcome, have cognitive impairment in the long-term. Since the pathogenesis of EBI, DCI and cognitive impairment remains unclear, no effective treatments are available to improve outcome. These data also stress the need to focus on other pathogenic processes that might be involved, such as reactive gliosis.

Reactive gliosis is a broad term, used for the acute response of astrocytes and microglia to a central nervous system injury, but also for the chronic reactivity state of these cells in neurodegenerative diseases. Classically reactive gliosis is seen as a scarring response, but this needs readjustment. Currently, reactive gliosis is recognized as a context dependent spectrum of heterogeneous multi-cellular responses [124]. Recent developments in glia biology have revealed that glial cells are versatile, they control the microcirculatory blood flow in the brain, contribute to synaptic plasticity by pruning and modifying synapses, and are actively involved in neuronal communication. The sustained activation state of astrocytes and microglia, which is a form of mild reactive gliosis after brain damage or during a degenerative disease, emerges as a contributing factor to cognitive decline [11,28,37,42].

Activation of astrocytes and microglia has also been implicated to be involved in vasospasm, microcirculatory vasoconstriction, edema, cortical spreading depression, and neuronal damage after SAH [40,53,119,148]. Therefore, reactive gliosis might be an important cellular process in the development of complications and long-term sequelae after SAH. In recent years, both preclinical and clinical studies have described the

Abbreviations: ADAMTS-13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; AQP1/4, Aquaporin 1/4; BBB, Blood Brain Barrier; BK, Big Potassium; CSD, cortical spreading depression; CSF, cerebrospinal fluid; DCI, delayed cerebral ischemia; EBI, early brain injury; ERK1/2, Extracellular signal-regulated protein kinases 1 and 2; ET-1, Endothelin-1; GABA, γ-aminobutyric acid; GFAP, Glial fibrillary acidic protein; Gln, Glutamine; GLT-1, Glutamate Transporter-1; GSN, Gelsolin; HMGB1, High Mobility Group Box-1; HO-1, Heme-Oxygenase-1; HSP47/70, Heat Shock Protein 47/70; IBA-1, ionized calcium-binding adapter molecule 1; IL-1α/1β/6/8/33, interleukin-1α/1β/6/8/33; iNOS, inducible Nitric Oxide Synthase; KIR4.1, inwardly rectifying potassium channel; LCA, Leukocyte Common Antigen; MAPk, Mitogen activated protein kinase; mGluR5, metabotropic Glutamate Receptor 5; MyD88, myeloid differentiation 88; NFκB, Nuclear Factor κB; Ngb, neuroglobin; OPN, Osteopontin; p-p38MAPK, phosphorylated p38 Mitogen-activated protein kinase; Pk-Cα, Protein Kinase Cα; RAGE, Receptor for Advanced Glycation End products; SAH, subarachnoid hemorrhage; SENP3, SUMO1/Sentrin/SMT3 Specific Peptidase 3; TGF-β, Transforming Growth Factor β; TLR4, Toll-Like Receptor 4.

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activation of glia induced by SAH. Here we review the literature on the glial response after SAH and its potential role in EBI, DCI and cognitive impairment after SAH. We performed a PubMed search on 13-07-2015 with the following search terms: ((‘microglia[MeSH Terms]’ OR ‘microgli*[Title/Abstract]’ OR ‘astrocytes[MeSH Terms]’ OR ‘astrogli*[Title/Abstract]’ OR ‘astrocyt*[Title/Abstract]’) AND (‘subarachnoid hemorrhage[MeSH Terms]’ OR ‘subarachnoid haemorrhage[Title/Abstract]’ OR ‘subarachnoid bleeding[Title/Abstract]’)). We included all research articles written in English that investigated an interaction between SAH and glial cells on a cellular and a molecular level *in-vivo* and *ex-vivo*.

2. Subarachnoid hemorrhage

2.1. Subarachnoid hemorrhage: pathophysiology

World-wide the incidence of SAH is 6–7 per 100,000 people per year and the median age it occurs is 55 years [137]. The incidence increases with age and women have a 1.6 times higher risk than men. The case fatality rate is high: about 35% of SAH patients die, including the 10–15% of patients who die before reaching the hospital [83]. Of those who survive, one-third needs lifelong care [129]. SAH is a type of stroke characterized by the extravasation of blood into the subarachnoid space of the brain. SAH can be caused by trauma or occur spontaneously, by the rupture of an aneurysm. In this review we will focus on spontaneous aneurysmal SAH that account for 85% of SAH cases. The prevalence of intracranial aneurysms in the general adult population is approximately 3% [101]. Intracranial aneurysms are usually located at arterial branch points at the base of the brain, mostly at bifurcations at the circle of Willis (Fig. 1). The most characteristic symptom of aneurysmal SAH is an acute and severe headache or neck pain, which mostly peaks within a few seconds after bleeding. SAH causes an abrupt increase in intracranial pressure, which causes a decrease in blood perfusion pressure. Blood pressure increases to balance the perfusion pressure, however, this is often not sufficient. Accordingly, the brain receives insufficient blood supply to function. Therefore, patients often have a decreased level of consciousness or focal neurological signs. These acute cerebral insults cause the onset of EBI [115].

2.2. Early brain injury

EBI is supposed to result from increased intracranial pressure, acute hydrocephalus, microvascular alterations, platelet aggregation, acute vasospasm, and reperfusion injury [8,116–118]. SAH also induces an increase in pro-inflammatory cytokines and reactive oxygen species and contributes to cell death of neurons, astrocytes, oligodendrocytes and endothelial cells [115]. Global cerebral edema occurs during the first 24 h after ictus [20]. Endothelin-1 and nitric oxide can induce microcirculatory vasoconstriction [115], which occurs in 70% of the arterioles within the first three days after SAH [30]. Moreover, microthrombi occlude arterioles, and are also evident at 3 hours [30]. Reactive gliosis is involved in several of the mechanisms contributing to EBI. Their potential role in these mechanisms will be discussed in Sections 3 and 4.

2.3. Delayed cerebral ischemia

DCI occurs in about 30% of surviving SAH patients [13,141]. These patients develop uni- or multifocal areas of ischemia, which are not

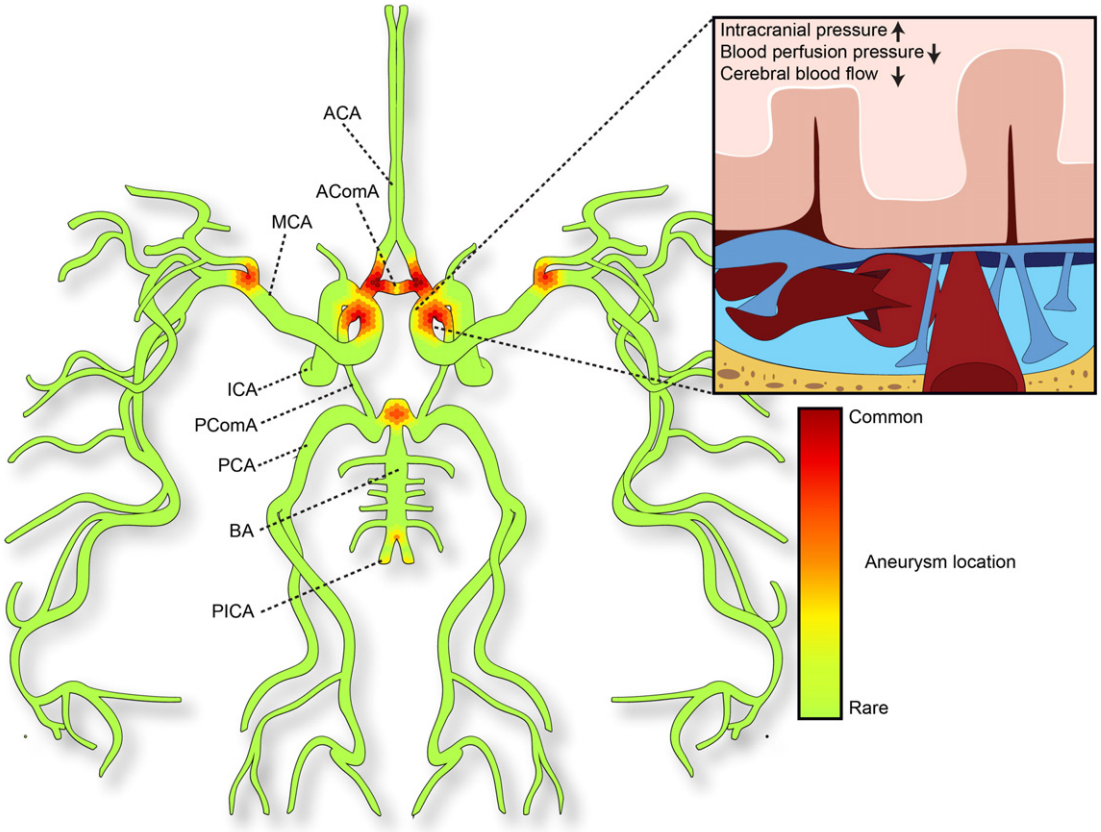

Fig. 1. Cerebral arterial vasculature and predilection sites of intracranial aneurysms. Basal view of the brains arteries. Aneurysms arise most frequently at the bifurcation of the anterior communicating artery (AComA), the middle cerebral artery (MCA), the posterior communicating artery (PComA) and the basilar artery (BA). Insert: In case of a ruptured aneurysm, blood flows into the subarachnoid space, causing increased intracranial pressure, reduced blood perfusion pressure, and reduced cerebral blood flow. Red color in the arteries indicates common locations of aneurysms, green color in the arteries indicates rare locations of aneurysms. ACA, anterior cerebral artery; ICA, Internal carotid artery; PCA, posterior cerebral artery; PICA, posterior inferior cerebellar artery.

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