Aneurysmal subarachnoid hemorrhage pathophysiology

A unifying theory for the pathophysiological changes following subarachnoid hemorrhage has yet not been described. Some of these changes may be causally connected or present themselves as an epiphenomenon of an associated process. A causal connection between DCI and early brain injury (EBI) would mean that future therapies should address EBI more specifically. If the mechanisms following SAH display no causal pathophysiological connection but are rather evoked by the subarachnoid blood and its degradation production, multiple treatment strategies addressing the different pathophysiological mechanisms are required. The discrepancy between experimental and clinical SAH could be one reason for unsuccessful translational results [1].

Many pathological mechanisms ensue after cerebral aneurysm rupture, including hydrocephalus, apoptosis of endothelial cells and neurons, cerebral edema, loss of blood brain barrier, abnormal cerebral autoregulation, microthrombosis, cortical spreading depression and macrovascular vasospasm.

There is significant theoretical evidence for the potential role of estrogen and progesterone use in altering the pathogenesis of SAH. Nevertheless, this has received mixed reviews in both case controlled studies and cohort analysis within the literature [2].

Gas chromatography, time-of-flight mass spectrometry was applied to CSF samples collected from 15 consecutive high-grade aneurysmal subarachnoid hemorrhage patients (modified Fisher grade 3 or 4). Collected CSF samples were analyzed at two time points (admission and the anticipated vasospasm timeframe). Metabolite levels at both time points were compared and correlated with vasospasm status and Glasgow Outcome Scale (GOS) of patients at 1 year post-aSAH. Significance level was defined as $p < 0.05$ with false discovery rate correction for multiple comparisons.

Of 97 metabolites identified, 16 metabolites, primarily free amino acids, significantly changed between the two time points. These changes were magnified in modified Fisher grade 4 compared with grade 3. Six metabolites (2-hydroxyglutarate, tryptophan, glycine, proline, isoleucine, and alanine) correlated with GOS at 1 year post-aSAH independent of vasospasm status. When predicting patients who had low disability (GOS 5 vs. GOS ≤4), 2-hydroxyglutarate had a sensitivity and specificity of 0.89 and 0.83 respectively.

This preliminary study suggests that specific metabolite changes occur in the brain during the course of aSAH and that quantification of specific CSF metabolites may be used to predict long-term outcome in patients with aSAH. This is the first study to implicate 2-hydroxyglutarate, a known marker of tissue hypoxia, in aneurysmal subarachnoid hemorrhage pathogenesis [3].

1)
van Lieshout JH, Dibué-Adjei M, Cornelius JF, Slotty PJ, Schneider T, Restin T, Boogaarts HD, Steiger HJ, Petridis AK, Kamp MA. An introduction to the pathophysiology of aneurysmal subarachnoid hemorrhage. Neurosurg Rev. 2017 Feb 18. doi: 10.1007/s10143-017-0827-y. [Epub ahead of print] Review. PubMed PMID: 28215029.

2)

Young AM, Karri SK, Ogilvy CS. Exploring the use of estrogen & progesterone replacement therapy in subarachnoid hemorrhage. Curr Drug Saf. 2012 Jul;7(3):202-6. Review. PubMed PMID: 22950381.

3)

Lu AY, Damisah EC, Winkler EA, Grant RA, Eid T, Bulsara KR. Cerebrospinal fluid untargeted metabolomic profiling of aneurysmal subarachnoid hemorrhage: an exploratory study. Br J Neurosurg. 2018 Dec 26:1-5. doi: 10.1080/02688697.2018.1519107. [Epub ahead of print] PubMed PMID: 30585503.