Invited Commentary on *TNF-R1 correlates with cerebral perfusion and acute ischemia following subarachnoid hemorrhage*

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The quest to identify accurate biomarkers of delayed ischemic neurologic deficit (DIND) after aneurysmal subarachnoid hemorrhage (aSAH) has been both daunting and, at times, bewildering due our incomplete understanding of the underlying mechanism of DIND. Historically DIND, and thus poor outcome after aSAH, was thought to be due to large vessel vasospasm. This view evolved as treatment trials addressing vasospasm failed to completely prevent DIND. In recent years, clinicians and investigators have recognized that large vessel spasm is likely only one of several pathways resulting in DIND[1]. It is widely believed that inflammation plays at least a partial role in the pathophysiology that results in DIND, which has resulted in intense study of inflammatory proteins as candidate predictive biomarkers. Produced by monocytes and macrophages, the inflammatory cytokine tumor necrosis factor alpha (TNF-a), is one such candidate. Levels of TNF-a in the blood[2] and in the cerebrospinal fluid[3], have been associated with poor outcome after aSAH, but not with angiographic vasospasm[2]. These observations provide one of many examples of the apparent disconnect between DIND and imaging findings.

In the above manuscript, the authors conducted a sub-analysis of a previously published prospective observational study of patients with aSAH, examining levels of TNF-a's main receptor, TNF-R1, and its relationship to perfusion imaging parameters and outcomes. In the original study, the authors measured TNF-R1 in the parent artery of the culpable aneurysm during endovascular securement, and in a concurrently drawn venous blood sample. They observed that venous levels of TNF-R1 were associated with outcome after aSAH, while arterial levels were associated with the development of hydrocephalus [4]. But in that investigation, the authors did not observe a relationship between DIND and levels of TNF-R1. Building on this work, the authors examined a subset of patients who underwent CT-perfusion within 72 hours after ictus from the trial, and recorded a number of perfusion parameters. Here, only one of these CT-perfusion parameters was associated with higher levels of TNF-R1: slower mean transit time (MTT). Additionally, none of the CT-perfusion parameters were associated with outcome. However, elevated levels of TNF-R1 were correlated with more diffusion restricting lesions (DWI) on MRI obtained in the first 72

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hours after ictus, and both TNF-R1 levels and DWI lesions independently associated with poor outcome (Modified Rankin score >2 at 6 months).

Taken together, this preliminary evidence suggests that the mechanism linking TNF-a or its primary receptor TNF-R1 to poor outcome does not appear to be reflected in perfusion imaging–in essence this is a negative study. We are again confronted by evidence of a disconnect between clinical outcome and imaging metrics of complication after aSAH. Two questions linger in the wake of this work; first: could TNF-R1 be an informative biomarker of poor outcome after aSAH? This association must be replicated and validated in a prospective, independent cohort of patients. Second, if poor large vessel perfusion is not the mechanism linking elevated levels of TNF-R1 and poor outcome, what is the mechanism? There is evidence that TNF-a may play a role in endothelial dysfunction, promoting aneurysmal growth and rupture[5], though the current investigation also included patients with non-aneurysmal, perimesencephalic SAH and demonstrated the same associations. A number of additional possibilities exist for future exploration, and include modulation of the microcirculation and spreading cortical depressions, among others. It also remains to be seen if modulation of the TNF-a signaling pathway might alter outcome, or if this is simply an epiphenomenon marking a worsened endotype. Regardless, as we endeavor to better stratify patients with aSAH, care must be exercised to disambiguate surrogate endpoints (e.g. imaging parameters) from clinical outcomes (e.g. functional scales), knowing that our understanding of DIND is incomplete.

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