Advances in the imaging of cerebral aneurysm inflammation

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ABSTRACT

Cerebral aneurysm formation, growth and rupture are thought to be the result of a complex interaction between cerebrovascular hemodynamics and pathobiology. Recently, new evidence has emerged regarding the role of inflammation in the walls of cerebral aneurysms. Noninvasive methods to characterize the degree of inflammation in aneurysms could enable clinicians to estimate the risk of future aneurysm growth and rupture, influencing treatment. This review examines emerging techniques of imaging inflammatory biomarkers in cerebral aneurysms.

Key words: Ferrosoferric oxide, inflammation, intracranial aneurysm, magnetic resonance angiography, subarachnoid hemorrhage

INTRODUCTION

Intracranial aneurysms are a substantial source of intracranial hemorrhage worldwide. Many aneurysms are detected incidentally, and the treatment calculus regarding unruptured aneurysms remains debatable. Early studies relied on aneurysm diameter, positing that small aneurysms nearly never ruptured;[1] however, recent data suggest that some small aneurysms confer a significant rupture risk.[2] More recently, complex morphologic and hemodynamic characteristics have been suggested to risk-stratify unruptured aneurysms for treatment.[3-5] Inflammation is related to hemodynamic stress,[6] but relying on only morphologic and hemodynamic factors alone does not account for the role of inflammation in the pathobiology of cerebral aneurysms.

Several studies have demonstrated that inflammation plays a key role in cerebral aneurysm formation and rupture.[7-9] Specifically, the role of macrophages in the response to inflammatory mediators has been proposed as a mechanism for aneurysm rupture.[10,11] However, these studies rely on histological analysis of aneurysm tissue.

Recently, the development of noninvasive imaging of inflammatory markers has been developed and applied to the study of cerebral aneurysms. Preliminary results are promising that the link between aneurysm rupture risk and inflammation is strong, and that such inflammation can be imaged in a clinical setting.

IMAGING OF MYELOPEROXIDASE

Myeloperoxidase, a potent bactericidal substance primarily housed in the granules of neutrophils, is present in the inflammatory environment. It is present in noninfectious inflammatory reactions such as those accompanying atherosclerosis[9] and vasculopathy.[12]

Gounis *et al*.[13] observed that increased myeloperoxidase expression in aneurysm tissue harvested during surgery was associated with all ruptured aneurysms, as well as those unruptured aneurysms that were considered "high-risk" for rupture based on demographic and anatomic characteristics. The same group has studied a paramagnetic agent (di-5-hydroxytryptamide of gadopentetate dimeglumine) that highlights the presence of myeloperoxidase in animal models of general vascular disease.[14] While no human studies of this magnetic resonance contrast agent have been performed, this represents a promising agent in the noninvasive detection of aneurysmal inflammation.

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IMAGING OF MACROPHAGE ACTIVITY

A recent sub-analysis of a large population-based prospective study of unruptured aneurysms demonstrated the protective effect of aspirin on the rupture risk of cerebral aneurysms.[15] The authors posit that the antiinflammatory effects of aspirin confer this risk reduction. In the presence of inflammation, the upregulation of cyclooxygenase-2 (COX-2) and microsomal prostaglandin E2 synthase-1 (mPGES-1) increases prostaglandin production, which in turn increases matrix metalloproteinase-9 (MMP-9) production by macrophages. This causes the degradation of proteins in the extracellular environment. This activity may lead to the weakening of the aneurysm wall, which when exposed to increased hemodynamic stress, leads to aneurysmal rupture.[5,6] Aspirin has been shown to attenuate the expression of COX-2 and mPGES-1, thus reducing the production of MMP-9 by macrophages.[16]

Histological studies of ruptured versus unruptured aneurysms have demonstrated an early (< 12 h) macrophage infiltrate, which some authors postulate may be responsible for an acute inflammatory reaction that precipitates aneurysm rupture.[8] The imaging of macrophage activity, therefore, could aid in the detection of a prerupture inflammatory state signaling aneurysm wall instability and urgent need for treatment.

Macrophage imaging has recently been piloted in humans in part due to the development of ferumoxytol. Ferumoxytol is a superparamagnetic form of iron oxide originally developed for the treatment of iron deficiency anemia.[17] Because ferumoxytol is detectable using conventional magnetic resonance imaging (MRI), and cleared by macrophagocytosis,[18] imaging after ferumoxytol infusion can highlight macrophage activity and hence inflammation.

The differential uptake of ferumoxytol infusion can be used to determine the degree of inflammatory activity of macrophages in cerebral vessels [Figure 1]. A histological study of unruptured aneurysms imaged using this modality prior to surgical resection detected iron particles as well as macrophage infiltration in the aneurysm wall, while only macrophages were detected in the tissue of a control group without ferumoxytol infusion.[19]

A further study of ferumoxytol correlated its early uptake on serial MRIs with impending aneurysm rupture.[20] Twenty-two patients with thirty unruptured aneurysms underwent MRI after ferumoxytol infusion at 3 time points: immediately, after 24 h, and after 72 h. The presence of ferumoxytol uptake was defined as a reduction in aneurysmal T2 signal when compared to baseline MRI. Ferumoxytol activity was defined as "early" if this change was detected in 24 h, and "late" if detected only 72 h after infusion. Fourteen aneurysms underwent subsequent surgical clipping, while sixteen were observed based on small aneurysm size, patient age or co-morbidity, or patient preference. Histological analysis was performed on all surgically treated aneurysms, as well as five ruptured aneurysms not imaged using ferumoxytol.

Among surgically repaired aneurysms with early uptake ($n = 4$), immunohistochemical analysis revealed COX-2, mPGES-1 and M1 macrophage activity similar to that of ruptured aneurysms. Those unruptured aneurysms with late uptake ($n = 5$) had significantly less COX-2 and mPGES-1 activity compared to both ruptured aneurysms and unruptured aneurysms with early ferumoxytol uptake.

Of the fourteen aneurysms not surgically treated, three demonstrated early signal changes, eight late

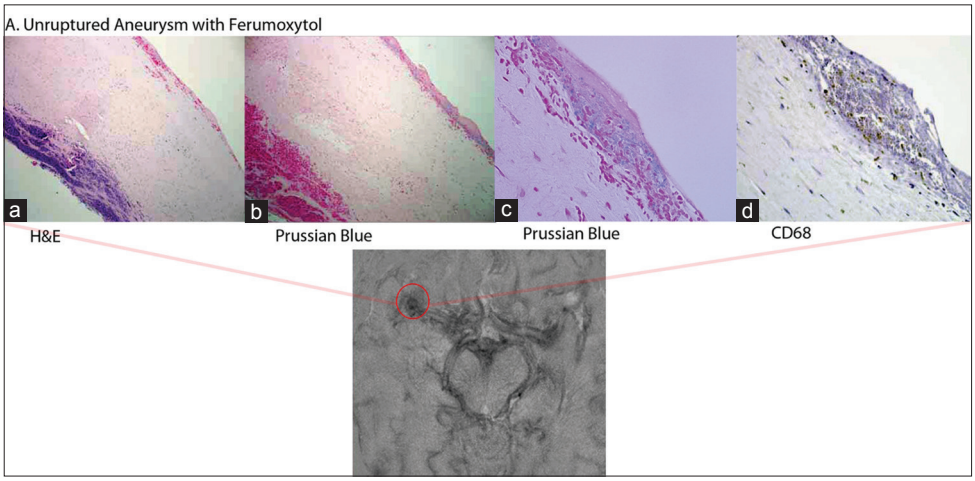

Figure 1: Histology and ferumoxytol-enhanced magnetic resonance imaging (MRI) of an unruptured middle cerebral artery (MCA) aneurysm: (a) HE ×100; (b) Prussian Blue stain showing iron oxide nanoparticles seen mostly in the adventitia; (c) higher magnification of Prussian blue stain demonstrating iron oxide nanoparticles; (d) CD68 showing positive staining for macrophages MRI illustrates right MCA aneurysm with ferumoxytol uptake. Figure adapted with permission from Hasan *et al*.[19]

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