Elucidating Sex Differences in Cerebral Aneurysm Biology and Therapy

The Time Is Now

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Subarachnoid hemorrhage remains a devastating disease despite improvements in the technology and techniques used in securing and obliterating ruptured aneurysms. As a result, there is evidence to treat unruptured cerebral aneurysms when found incidentally or in the setting of symptoms suggestive of impending rupture. At present, there are no accepted medical therapies that reduce the risk of rupture or lead to aneurysm obliteration. Endovascular and microsurgical treatments continue to be the standards of care but are invasive and not without significant risk. This potential risk is magnified when treating an aneurysm prophylactically, considering it may remain asymptomatic for the entirety of the life of the patient. The widespread availability of highly sensitive noninvasive imaging modalities, such as magnetic resonance angiography and computed tomographic angiography, has greatly increased the number of unruptured aneurysms diagnosed each year. Thus, more now than ever, clinicians are faced with the challenging scenario of managing an unruptured asymptomatic aneurysm. As a result, noninvasive medical therapies that could reduce or eliminate the risk of aneurysm rupture are of great interest.

At the heart of developing effective medical therapies is an improved understanding of the mechanisms underlying cerebral aneurysm formation and rupture. The role of inflammation in the development and rupture of cerebral aneurysms has been clearly established based on burgeoning data derived from human and animal studies. An enhanced understanding of the inflammatory mediators contributing to the pathogenesis of cerebral aneurysms has facilitated the identification of targeted therapies. Hasan et al identified aspirin as a therapeutic agent that may reduce the risk of cerebral aneurysm rupture. Aspirin is a particularly attractive therapy because it has well-established anti-inflammatory effects, is inexpensive, is widely available, and has an acceptable safety profile. Furthermore, it is commonly used in the patient population with vascular pathology and is a routine component of treatment for coronary artery disease, stroke, and peripheral vascular disease. As a result, aspirin represents a promising agent for the noninvasive treatment of unruptured cerebral aneurysms.

The literature continues to highlight the influence of sex on human disease, particularly the mechanisms, presentation, and management of ischemic heart disease. It is well known that cerebral aneurysms have a higher prevalence in women compared with men (prevalence ratio of 1.61 [1.02–2.54] overall and a prevalence ratio of 2.2 [1.3–3.6] in populations with a mean age ≥50 years). The incidence of subarachnoid hemorrhage is also higher in females compared with males. Preliminary work has investigated a role for estrogen in mitigating subarachnoid hemorrhage. The strength of this article is found in its examination of the effects of sex on the biochemical processes mitigating aneurysm rupture.

The authors used human data from the International Study of Unruptured Intracranial Aneurysms to determine if sexual dimorphism exists in response to human cerebral aneurysms to aspirin. The authors found that the proportion of subarachnoid hemorrhage in males using aspirin ≥3 times per week to daily (6%) was significantly lower than the proportion in males using aspirin less frequently (47%; P<0.05). In contrast to the male cohort, the proportion of subarachnoid hemorrhage cases in females using aspirin ≥3 times per week to daily (16%) did not differ from females who used aspirin less frequently (29%; P=0.05).

The authors investigated the aspirin effect in mice to elucidate potential protective mechanisms and also to investigate a potential sex difference in aspirin response. The incidence of aneurysm rupture was significantly lower, and survival was significantly higher in the aspirin-treated and cyclooxygenase-2 (COX 2) inhibitor–treated groups. Additionally, expression of matrix metalloproteinase-9, which has been shown to degrade cerebral aneurysm walls, was diminished in the aspirin and COX-2 inhibitor groups. Examination of COX-1 knockout and mPGES-1 (microsomal prostaglandin E synthase-1) knockout mice suggested that the protective effects of aspirin are likely mediated through COX-2 inhibition rather than through COX-1 inhibition. The authors next examined a sex differential response to aspirin in mice. The incidence of cerebral aneurysm rupture was significantly lower in male mice. Furthermore, expression of 15-hydroxyprostaglandin dehydrogenase (15-PGDH) was significantly higher in male mice, whereas COX-2, CD-68, matrix metalloproteinase-9, MCP-1 (monocyte chemoattractant protein-1), and NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells) expression were significantly higher in female mice.
Perhaps the most important finding to come from this article is the data on differential expression of 15-PGDH between male and female mice. This enzyme converts prostaglandin E\textsubscript{2} (PGE\textsubscript{2}) to 15-keto-PGE\textsubscript{2}, a peroxisome proliferator-activated receptor \(\gamma\) (PPAR \(\gamma\)) agonist. PPAR \(\gamma\) agonists have been previously shown to reduce the incidence of aneurysm formation and rupture. Aspirin may activate 15-PGDH, which increases 15-keto-PGE\textsubscript{2} activity and further reduces the incidence of aneurysm rupture. B. The sex difference in aneurysm rupture is abolished when under physiological conditions 15-PGDH converts PGE\textsubscript{2} to 15-keto-PGE\textsubscript{2}, a PPAR \(\gamma\) agonist. PPAR \(\gamma\) agonists have been previously shown to reduce the incidence of aneurysm formation and rupture. Aspirin may activate 15-PGDH, which increases 15-keto-PGE\textsubscript{2} activity and further reduces the incidence of aneurysm rupture. C. Female mice treated with aspirin and a 15-PGDH activator demonstrates an increase in 15-keto-PGE\textsubscript{2} activity and experiences a significantly lower risk of aneurysm rupture when compared with mice treated with aspirin alone.

Figure. A. Under physiological conditions, 15-hydroxyprostaglandin dehydrogenase (15-PGDH) converts prostaglandin E\textsubscript{2} (PGE\textsubscript{2}) to 15-keto-PGE\textsubscript{2}, a peroxisome proliferator-activated receptor \(\gamma\) (PPAR \(\gamma\)) agonist. PPAR \(\gamma\) agonists have been previously shown to reduce the incidence of aneurysm formation and rupture. Aspirin may activate 15-PGDH, which increases 15-keto-PGE\textsubscript{2} activity and further reduces the incidence of aneurysm rupture. B. The sex difference in aneurysm rupture is abolished when under physiological conditions 15-PGDH converts PGE\textsubscript{2} to 15-keto-PGE\textsubscript{2}, a PPAR \(\gamma\) agonist. PPAR \(\gamma\) agonists have been previously shown to reduce the incidence of aneurysm formation and rupture. Aspirin may activate 15-PGDH, which increases 15-keto-PGE\textsubscript{2} activity and further reduces the incidence of aneurysm rupture. C. Female mice treated with aspirin and a 15-PGDH activator demonstrates an increase in 15-keto-PGE\textsubscript{2} activity and experiences a significantly lower risk of aneurysm rupture when compared with mice treated with aspirin alone.

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There are important limitations to the study that should be discussed. As the authors point out, there remains some question as to whether the murine aneurysm model accurately mimics the human disease. Speaking from experience, intracranial aneurysms are often found to be complex lesions at surgery. The walls may be calcified and atherosclerotic, evidence that these lesions have taken quite some time to develop. Additionally, the great variability between lesions suggests multiple underlying processes leading to development and rupture in humans. It is likely that the cascade of biomechanical and cellular processes at work in the humans are more diverse and long standing when compared with the simplified mechanisms by which these mice develop aneurysms. The aspirin dose required to prevent aneurysm rupture in humans needs to be further explored. In this study, the murine dose of aspirin was disproportionately high compared with the 325 mg dose in humans from the International Study of Unruptured Intracranial Aneurysms. It would also be interesting to determine if varying the dose of aspirin could overcome the sex differences in response. Similarly, determining if COX-2 inhibitors demonstrate a sex difference in response would be interesting.

Despite significant clinical data demonstrating the impact of sex on cerebral aneurysm incidence and rupture, this important variable had been largely neglected. This work is indicative of the need for a comprehensive understanding of sex differences in cerebrovascular disease.

Disclosures
None.

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