Search for Biomarkers of Intracranial Aneurysms: A Systematic Review

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Key words
- Biomarker
- Intracranial aneurysm
- Subarachnoid hemorrhage
- Systematic review

Abbreviations and Acronyms
A1AT: Alpha-1-Antitrypsin
ACE: Angiotensin-converting enzyme
ADMA: Asymmetric dimethylarginine
APOE: Apolipoprotein E
CAM: Cellular adhesion molecules
CSF: Cerebrospinal fluid
eNOS: Endothelial nitric oxide synthase
GM-CSF: Granulocyte-monocyte colony-stimulating factor
GOS: Glasgow Outcome Score
IA: Intracranial aneurysm
ICAM: Intercellular adhesion molecule
IL: Interleukin
LOI: Lactate-oxygen index
LPA: Lipoprotein A
MCP: Monocyte chemoattractant protein
MPO: Myeloperoxidase
MR: Metabolic ratio
NfHSM135: Neurofilament heavy chain SM135
NOS: Nitric Oxide Synthase
PECAM: Platelet endothelial cell adhesion molecule
RA: Ruptured aneurysms
SAH: Subarachnoid hemorrhage
TNF: Tumor necrosis factor
TSH: Thyroid-stimulating hormone
UA: Unruptured aneurysm
VCAM: Vascular cell adhesion molecule
VEGF: Vascular endothelial growth factor

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■ INTRODUCTION: **Intracranial aneurysms (IAs) remain a devastating clinical challenge, and the pathogenesis of IA formation and progression continues to be unclear. Biomarker analysis can help us understand IA development. The authors performed a systematic review of current literature on genetic and serum biomarkers for IAs in an attempt to identify diagnostic/prognostic factors for ruptured and unruptured aneurysms.**

■ METHODS: **All relevant studies on PubMed that reported blood/cerebrospinal fluid (CSF) biomarkers and genes that regulate biomarker levels for IAs were assessed for whether the biomarkers/genes studied correlated with IA formation and rupture.**

■ RESULTS: **Thirty-three studies were reviewed. IAs are associated with an increase in levels of immunologic markers, particularly complement C3 and C9, immunoglobulins IgG and IgM, M1/M2 macrophages, monocytes, and B and T lymphocytes; increase in blood and CSF levels of adhesion molecules; selectins found on vascular endothelium, platelets, and leukocytes; doubled ratios of elastase-to–alpha-1-antitrypsin as controls; elevated levels of neurofilament heavy chain SM135 and S-100 post rupture; and locus 19q13 with many candidate genes.**

■ CONCLUSION: **Though the pathophysiology of the disease remains unclear, the current literature supports the role of inflammatory and cell adhesion molecules, enzymes and hormones that effect cerebral vasculature, and other cerebral proteins related to brain and vascular damage in both the formation and progression to rupture of IAs. Future investigations are needed to validate results from previous studies and identify new diagnostic/prognostic biomarkers of IAs.**

INTRODUCTION

Intracranial aneurysms (IA) are cerebrovascular lesions characterized by weakening and abnormal dilatation of cerebral arteries (7, 40, 42). They occur in about 0.4%–6% of the population worldwide (7, 8, 14, 16, 19, 23). The majority of IAs present as a single aneurysm (70%–75%) and are located at the bifurcation of major cerebral arteries, most commonly at the internal carotid-posterior communicating artery and anterior cerebral-anterior communication artery junctions (8, 14, 40). Although the International Study of Unruptured Intracranial Aneurysms (ISUIA) and the Unruptured Cerebral Aneurysm Study of Japan (UCAS Japan) show the overall risk of IA rupture is small (1, 13) (~<1% risk annually and ~10% prevalence compared with unruptured aneurysms [UAs]), rupture results in subarachnoid hemorrhage (SAH), which is associated with a high mortality rate (25%–50%) (3, 7, 9, 19, 23, 27, 29, 33). Moreover, 40%–60% of survivors suffer severe disability (2, 3, 8, 9, 15, 16, 19, 23, 24, 29, 31). Importantly, if IAs are diagnosed and surgically treated before rupture, mortality and morbidity rates decrease drastically to as low as 0%–2.5% (2, 15, 31).

Given the devastating consequences of subarachnoid hemorrhage, early recognition and treatment of IAs before rupture is paramount. Unfortunately, 85%–90% of UAs are asymptomatic (16). Genetic and environmental factors, such as hypertension, smoking, alcohol consumption, female gender, and age >50 years, have been associated with an increased chance of harboring an IA (2, 8, 16, 19, 23, 33, 37, 42); however, even in the presence of such risk factors, IA formation and rupture are extremely hard to predict and stage because the pathogenesis of IA is unclear. Therefore the analysis of

biomarkers can help us understand IA formation and progression, which can be crucial to help prevent the devastating consequences of rupture and improve patient management (2, 20, 31).

The aim of this study is to identify diagnostic and/or prognostic factors for ruptured and unruptured IAs. To this purpose, we performed a systematic review of the current literature for the analysis of genetic and serum biomarkers of IAs development and progression to rupture.

MATERIALS AND METHODS

Study Selection

Using the MeSH database system of PubMed, a literature search was performed between the years 1994 and 2014 for all articles containing the terms *intracranial aneurysm* and *biological markers* (*"Intracranial Aneurysm"[Mesh] AND "Biological Markers"[Mesh]*). The articles were limited to English with humans as the only subjects of this study.

Clinical studies and case reports were included, while reviews, editorials, and commentaries were excluded. The initial inclusion criteria focused mainly on searching for blood and cerebrospinal fluid (CSF) biomarkers for unruptured and ruptured cerebral aneurysms. Articles regarding genes coding for blood and CSF biomarkers or enzymes controlling biomarker levels were also included, while those about histologic markers not related to blood or CSF biomarkers were excluded. Thirty articles were identified from this initial screen. An additional 3 papers were obtained from a brief search on other databases using the same criteria to include studies of important biomarkers not found through the initial search.

Duplicate studies were not found. The last MeSH search was performed July 5, 2014. A flow chart of the number of articles screened can be seen in **Figure 1**.

Data Extraction

The included studies were analyzed carefully on the basis of patient population, diagnosis, and biomarker. The studies were separated into groups according to whether they assessed blood and/or CSF biomarkers, genes and susceptible loci with candidate genes for biomarkers, and genes coding for enzymes that regulate levels of biomarkers in both unruptured and ruptured cerebral aneurysms. Studies assessing blood and/or CSF biomarkers were further divided into those discussing possible biomarkers of unruptured and ruptured aneurysms (RAs). The articles were assessed for whether or not the biomarkers and/or genes studied correlated with intracranial aneurysm formation, growth, and rupture. Data for all patients were reported when available in the literature.

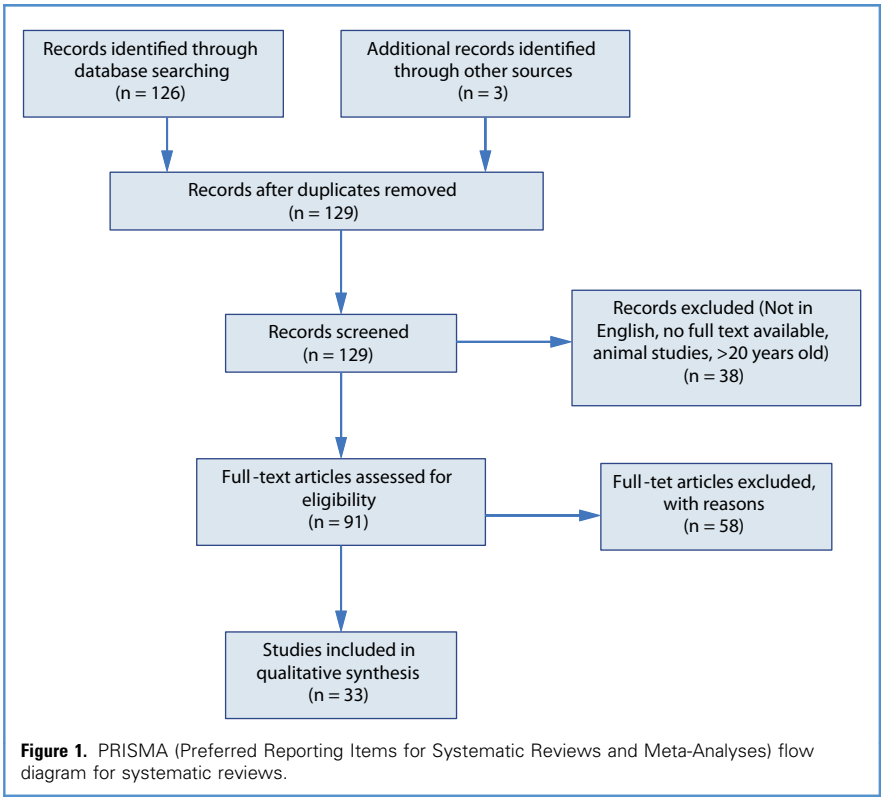

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for systematic reviews.

RESULTS

Study Selection

After screening the articles found for the parameters described earlier, 33 studies were included in our review. Before further analyses, articles were divided into different categories on the basis of the method used to identify potential biomarkers for IA formation and rupture.

Biomarkers in Unruptured Aneurysms

Eight studies analyzed blood biomarkers for UAs (**Table 1**). Five of them assessed blood directly (2, 31, 33), whereas 3 performed an immunohistochemical analysis of collected aneurysm tissue for the identification of proteins predictive of blood biomarkers (8, 12). It was shown that the ratios between serum elastase and alpha-1-antitrypsin (A1AT) levels in patients with ruptured and UAs were twice as high as those of controls ($P < 0.05$) (2). A different study reported that 10 out of 11 patients with asymptomatic aneurysms had elevated serum lipoprotein A (LPA) levels compared with controls (31) (53.7 ± 1.2 mg%, aneurysmal subjects vs. 22.1 ± 1.45 mg%, subject with aneurysm family history vs. 10.5 ± 0.48 mg% control subjects, $P < 0.05$) (31). Serum vascular endothelial growth factor (VEGF) levels were measured in 46 patients, and levels were significantly higher among the male aneurysm group than in controls but not in the female group (33). Interestingly, VEGF levels in females only correlated with age, but not with the presence of aneurysms. It is important to note that VEGF levels did not correlate with the number and location of aneurysms (33). Plasma cytokine levels were also