Review Article

Intracranial Large and Medium Artery Atherosclerotic Disease and Stroke

Sami Al Kasab, MD,* Colin P. Derdeyn, MD,† Waldo R. Guerrero, MD,* Kaustubh Limaye, MD,* Amir Shaban, MD,* and Harold P. Adams Jr, MD*

Background: Intracranial atherosclerotic disease (ICAD) is one of the most common causes of stroke worldwide and is associated with a high risk of stroke recurrence. We sought to perform a literature review of the epidemiology, pathophysiology, and treatment options. *Methods:* A literature review on recent studies evaluating the epidemiology, risk factors, clinical presentation, and treatment was reviewed. ICAD is particularly common in Africa and Asia. *Results:* Although the medical management of ICAD has improved over the past decade, a subgroup of patients with ICAD remains at significantly high risk of stroke recurrence, and newer studies that aim at improving our understanding of ICAD and evaluating new treatment methods are currently under way. *Conclusion:* ICAD remains a common cause of stroke worldwide; further studies evaluating treatment options to prevent stroke recurrence are urgently needed. **Key Words:** Ischemic stroke—intracranial atherosclerosis—large and medium-sized arteries—recurrent stroke.

Introduction

Worldwide, intracranial atherosclerotic disease (ICAD) is among the leading causes of ischemic stroke. For this review, the term ICAD encompasses the disease of major intracranial arteries (intracranial vertebral, intracranial internal carotid, basilar, and proximal segments of the middle cerebral artery [MCA; M1], anterior cerebral artery [ACA; A1], and posterior cerebral artery [PCA; P1]). It also includes atherosclerotic lesions of larger branches of the previously described major intracranial arteries. Such segments as the M2 or 3 of the MCA, A2 or 3 of the ACA, and the P2 or 3 of the PCA also are included. It does not include micro-atherosclerotic disease that may affect small penetrating arteries, which are associated with the traditional lacunar syndromes. Recent studies provide insights on the diagnosis and management of patients with ICAD. In this review, we discuss the epidemiology, risk factors, clinical presentations, evaluation, prognosis, and treatment of patients with symptomatic large artery ICAD.

Epidemiology

The prevalence of symptomatic large artery ICAD in the literature ranges from 20% to 53% depending on the study population and study methods.[1] ICAD is more prevalent in Asia, Africa, South America, and the Middle East than in Europe or North America.[2] It is responsible for 8%-10% of ischemic strokes in North America and for 30%-50% of ischemic strokes in Asia[3,4] In a postmortem study in China, ICAD greater than 50% was found in 30%-50% of subjects.[5] In the United States, ICAD is also

From the *Division of Cerebrovascular Diseases, Department of Neurology; and †Department of Radiology, Carver College of Medicine, UIHC Comprehensive Stroke Center, University of Iowa, Iowa City, Iowa.

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Address correspondence to Harold P. Adams Jr, MD, Department of Neurology, University of Iowa, 200 Hawkins Drive, Iowa City, IA 52242. E-mail: Harold-Adams@uiowa.edu.

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more common among African-Americans than in whites.[5-7] In the Northern Manhattan Stroke study, ICAD-related strokes accounted for 9%, 15%, and 17% of all ischemic strokes among white, Hispanic, and African-American patients, respectively.[8] The reasons why ICAD is more common in Asians, Hispanics, and African-Americans remain unknown. Possible explanations include the presence of inherited and acquired susceptibility of intracranial vessels to atherosclerosis or differences in response to risk factor control.[9-12] The high prevalence of ICAD among African-Americans may be partly attributed to the high rates of hypertension, hyperlipidemia, and diabetes mellitus (DM), which are well-known risk factors associated with accelerated ICAD.[13] However, rates of hypertension, DM, and hyperlipidemia are comparable with those of whites in the Chinese population.[14] This finding raises the possibility of genetic or environmental factors that contribute to the different rates of ICAD in the two groups.[14] Conversely, the prevalence of extracranial atherosclerotic disease is much higher among whites in the United States, and similar high rates are found in Europe. Further research into the factors that influence the location of atherosclerotic disease in the cerebral vasculature among different ethnic groups and geographic populations is needed.

Risk Factors and Associated Diseases

The traditional risk factors for accelerated ICAD include hypertension, DM, hyperlipidemia, smoking, and advanced age. ICAD is more commonly found in men than in women.[15,16] When ICAD affects men, it most commonly involves the basilar artery.[17] Previous studies have shown that men have a higher rate of ICAD in their fourth and fifth decades compared with women, whereas women do not have significant ICAD until their sixth decade.[18,19] The explanation for this sex difference in ICAD remains unclear; it has been speculated that it could be related to the risk factor profile differences, namely the influence of sex hormones on blood pressure (BP) and cholesterol levels.[20] Age, hypertension, and diabetes are independent risk factors of symptomatic as well as asymptomatic ICAD.[18] Large-scale autopsy studies show that the changes in atherosclerosis progress with age.[18,21] Compared with extracranial atherosclerosis, ICAD develops close to 20 years later in life.[22] ICAD has been shown to be most commonly seen in the sixth and seventh decades, with a steady increase beyond the eighth decade.[23] Hypertension is correlated with the degree of ICAD in different ethnic groups.[24,25] Hypertension has been shown to be more prevalent in African-Americans, which could partly explain the higher incidence of ICAD in this ethnic group. Metabolic syndrome is also independently associated with ICAD.[26] In 1 study, analysis of the of the metabolic syndrome components, elevated BP, hyperglycemia, and abdominal obesity were found to be each independently associated with ICAD.[27] While dyslipidemia is an established risk factor for coronary artery disease, its role in ICAD is not as clear.[28,29] Elevated low-density lipoprotein (LDL) levels are associated with extracranial atherosclerosis, whereas elevated levels of oxidized LDL, a high ratio of apolipoprotein B to apolipoprotein I, and low levels of apolipoprotein AI are associated with ICAD.[19,30,31] Physical activity and lifestyle modification, which have not received much attention in stroke prevention trials, are associated with lower risk of stroke among medically treated patients with an ICAD.[32,33] Extensive atherosclerotic coronary artery disease is also associated with ICAD.[5,34,35] In a study of patients with symptomatic ICAD, 52% were also diagnosed with silent myocardial ischemia due to atherosclerosis.[36]

Mechanisms of Stroke in ICAD

There are 3 main mechanisms of ischemic stroke due to ICAD: (1) hypoperfusion; (2) branch atheromatous disease; and (3) artery-to-artery embolism.[37-39] Each of these mechanisms carries a different prognosis, risk of recurrence, and response to treatment.[40,41] The stroke pattern in ICAD depends on the underlying mechanism and can be classified as follows: (1) a perforator-subcortical pattern that usually results from the occlusion of the perforator origin at the site of ICAD; (2) a territorial pattern that is thought to result from artery-to-artery embolism or in situ thrombo-occlusion; (3) a border-zone pattern that results from hypoperfusion; and/or (4) a mixed pattern that results from the combination of more than 1 mechanism.[42,43] While stroke pattern on brain imaging can help with identifying the mechanism of stroke in ICAD, stroke patterns are often not as clear and mixed, limiting the clinician's ability to accurately identify the exact mechanism of stroke in patients with ICAD.

Previous studies performed among patients with ICAD have shown different frequencies of these stroke patterns. A post hoc analysis of the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial showed that the most common pattern of infarction was border-zone (52.4%), followed by territorial (23.8%), and perforator (23%).[44] Patients with border-zone infarctions as their qualifying events were at highest risk of stroke recurrence.[43] However, analysis of the Warfarin–Aspirin Symptomatic Intracranial Disease (WASID) trial data showed that the most common infarction pattern was territorial (50.7%), followed by perforator (25%), mixed (15.5%), and border-zone (8.8%).[42] The difference is thought to be due to the fact that in SAMMPRIS enrolled subjects had to have ≥70 stenosis, whereas in WASID the threshold was ≥50%.[44]

Clinical Presentations of ICAD

The clinical presentations of stroke due to underlying ICAD vary depending on the underlying mechanism.