Review Article

Intracranial Arterial Stenosis

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Intracranial arterial stenosis (IAS) is usually attributable to atherosclerosis and corresponds to the most common cause of stroke worldwide. It is very prevalent among African, Asian, and Hispanic populations. Advancing age, systolic hypertension, diabetes mellitus, high levels of low-density lipoprotein cholesterol, and metabolic syndrome are some of its major risk factors. IAS may be associated with transient or definite neurological symptoms or can be clinically asymptomatic. Transcranial Doppler and magnetic resonance angiography are the most frequently used ancillary examinations for screening and follow-up. Computed tomography angiography can either serve as a screening tool for the detection of IAS or increasingly as a confirmatory test approaching the diagnostic accuracy of catheter digital subtraction angiography, which is still considered the gold (confirmation) standard. The risk of stroke in patients with asymptomatic atherosclerotic IAS is low (up to 6% over a mean follow-up period of approximately 2 years), but the annual risk of stroke recurrence in the presence of a symptomatic stenosis may exceed 20% when the degree of luminal narrowing is 70% or more, recently after an ischemic event, and in women. It is a matter of controversy whether there is a specific type of treatment other than medical management (including aggressive control of vascular risk factors and antiplatelet therapy) that may alter the high risk of stroke recurrence among patients with symptomatic IAS. Endovascular treatment has been thought to be helpful in patients who fail to respond to medical treatment alone, but recent data contradict such expectation. **Key Words:** Atherosclerosis—intracranial arterial stenosis—middle cerebral artery stenosis—middle cerebral artery stroke—epidemiology—vascular risk factors—pathophysiology—neuroimaging—management and treatment.

Introduction

Intracranial arterial stenosis (IAS) corresponds to luminal narrowing of large intracranial arteries. IAS is most often attributable to primary atherosclerosis, although embolic events can occasionally result in severe stenosis. Other causes of IAS include arterial dissection, inflammatory disorders (vasculitis), infections of the central nervous system, radiation, sickle cell disease, and moyamoya disease or moyamoya syndrome.[1]

IAS is the most common cause of stroke worldwide.[2,3] The widespread use of noninvasive or minimally invasive neuroimaging techniques, such as transcranial

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Doppler (TCD) and magnetic resonance angiography (MRA) or computed tomography angiography (CTA), has increased the detection of this type of pathology.

IAS may involve any intracranial vessel and may concomitantly occur in patients with stenosis in extracranial arteries, namely in the extracranial part of the internal carotid artery (ICA) or the vertebrobasilar system. The present work aims at reviewing the state of the art concerning atherosclerotic IAS with a particular emphasis on stenosis of the middle cerebral artery (MCA), which is the main intracranial artery perfusing the cerebral hemispheres.

Epidemiology and Risk Factors

IAS is far more prevalent in Asian and African subjects and in subjects of Hispanic origin.[4] By using TCD, population-based studies in China revealed asymptomatic intracranial arterial disease in 5.9%-6.9% of subjects over the fifth decade of life.[5,6] A cross-sectional study using TCD in Hong Kong found asymptomatic IAS in 12.6% of the included cases.[7] One study using MRA in Japan found asymptomatic IAS in 14.7% of subjects referred to a neurology clinic because of concerns about a possible stroke.[8] IAS is more severe in black people than in other populations. Black subjects with IAS are at higher risk of stroke recurrence than whites.[9]

Although studies addressing possible gender differences provided conflicting results on the prevalence and severity of IAS among asymptomatic subjects,[5,10] women with symptomatic IAS enrolled into the Warfarin–Aspirin Symptomatic Intracranial Disease (WASID) trial[11] were found to have greater risk of stroke and death than men.[12]

Different vascular risk factors may be associated with different locations of IAS.[13,14] In general, potentially modifiable risk factors for intracranial atherosclerosis include hypertension, smoking, diabetes, and dyslipidemia—high total cholesterol, high low-density lipoprotein cholesterol, and low high-density lipoprotein cholesterol.[5,10,15] Nonmodifiable risk factors include race, age, certain angiotensin-converting enzyme polymorphisms, an increased plasma endostatin/vascular endothelial growth factor ratio, the glutathione S-transferase omega-1 gene polymorphism, and increased levels of plasma homocysteine.[4] Metabolic syndrome is also associated with IAS. It occurs in approximately 50% of the subjects with symptomatic intracranial atherosclerotic disease and is associated with substantially higher risk of major vascular events.[16-18]

An association between Alzheimer disease and intracranial atherosclerosis has been described.[19,20] It is also conceivable that IAS in itself might be a specific cause of vascular cognitive impairment. Furthermore, there is an increasing awareness that both cerebrovascular and neurodegenerative pathology may concomitantly occur very often[21] and that there are common risk factors for each of them.[22]

Pathophysiology and Clinical Expression

IAS may cause transient or definite neurological symptoms or can be clinically asymptomatic, depending on severity of IAS, reversibility of the potentially associated ischemia, or on the efficiency of arterial collateralization. Possible mechanisms of cerebral infarction secondary to IAS include hemodynamic compromise distal to the site of stenosis, *in situ* thrombosis leading to complete artery occlusion, artery-to-artery embolism, perforating local branch occlusion, or a combination.[23]

Chronic cerebral hypoperfusion secondary to asymptomatic IAS may confer risk of stroke[24] because of decreased washout of small emboli[25] or of potential disruption of cerebral autoregulation. In normal conditions, homeostatic mechanisms corresponding to cerebral autoregulation tend to minimize changes in cerebral blood flow (CBF) secondary to variation of the perfusion pressure. To maintain CBF, cerebral autoregulation mostly relies on the capacity of the precapillary vascular wall to contract or distend, causing changes in vessel diameter. Brain arterioles can dilate and increase the corresponding blood flow in response to several stimuli (eg, hypercapnia secondary to breath holding, acetazolamide, or CO_2 inhalation), a process called vasoreactivity.[26,27] In the presence of severe IAS, compensatory vasomotor mechanisms work up to their limit, leading to a maximum distension of the vascular wall. If such a limit is exceeded, the stenosis may become symptomatic because of a lack of cerebral perfusion pressure, and it is expected that any additional vasodilator stimuli will not lead to an increase of perfusion in the corresponding vascular territory. In other words, cerebral vasoreactivity might become compromised in the presence of a high-grade arterial stenosis or occlusion. Therefore, patients with impaired cerebral vasoreactivity and severe IAS may be at higher risk of subsequent stroke, similar to patients with impaired cerebral vasoreactivity in association with asymptomatic extracranial carotid stenosis or occlusion.[28] Asymptomatic stenoses might also become symptomatic, through a hemodynamic mechanism, when a subject with severe IAS is submitted to a long period of hypotension (eg, after heart attack, trauma, or surgery). Computed tomography and magnetic resonance (MR) perfusion, single-photon emission computed tomography, and positron emission tomography studies have been used to evaluate vasoreactivity and cerebrovascular reserve in patients with IAS, but the ability of those examinations to predict future stroke risk in such patients is yet to be determined.[24,29-33]

Lesions involving the MCA, basilar artery, or the intracranial vertebral artery are more likely to be symptomatic, whereas lesions occurring in the territory of anterior or posterior cerebral arteries are often asymptomatic.[13] The *Groupe d'Etude des Sténoses Intra-Crâniennes Athéromateuses Symptomatiques* study[34] and a study by Sánchez-Sánchez