Large Artery Intracranial Occlusive Disease: A Large Worldwide Burden but a Relatively Neglected Frontier

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Stroke 2008;39;2396-2399; originally published online Jun 5, 2008;
DOI: 10.1161/STROKEAHA.107.505776
Stroke is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0039-2499. Online ISSN: 1524-4628

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A Large Worldwide Burden but a Relatively Neglected Frontier

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***Background and Purpose*—**Large artery intracranial occlusive disease (LAICOD) is a common and important stroke subtype. In this commentary, we review key epidemiological aspects of LAICOD.

***Summary of Review*—** LAICOD has emerged as the most common stroke subtype worldwide and is associated with a high risk of recurrent stroke. Hypotheses have been proposed to explain causation, which include such factors as traditional cardiovascular risk factors, high blood volume states, and genetic abnormalities. Approaches to treatment such as antithrombotic therapies, revascularization procedures, and counterpulsation devices hold promise.

***Conclusions*—**LAICOD poses a major stroke problem worldwide and is likely the most common stroke subtype. The etiology and treatment of this disorder remain poorly defined. International collaborations are needed to pool collective knowledge and develop definitive studies to better understand causation and treatment of LAICOD. **(*Stroke*. 2008;39: 2396-2399.)**

Key Words: intracranial occlusive disease ■ risk factors ■ high-risk populations

Large artery intracranial occlusive disease (LAICOD) has emerged as a well-defined stroke subtype.[1,2] As a well-defined and prevalent stroke subtype, LAICOD serves as an important target for prevention and treatment. It had received relatively little attention in the United States and North America, however, until it became better known in the late 1950s and 1960s. This was based on a series of brain autopsy studies in the south of the United States and the International Atherosclerosis Project,[3,4] conventional cerebral angiographic studies that we carried out in the 1980s among a racially mixed, hospital, referral-based population in Chicago, Ill,[5–7] and the international Extracranial-Intracranial Bypass Trial of the 1980s.[8] More recently, the importance of LAICOD has been highlighted by the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) study[9] and novel treatment approaches for this disorder such as angioplasty and stenting.[10] Overall, LAICOD has been a relatively neglected disorder because many have and continue to focus on the more accessible extracranial carotid artery occlusive disease lesion. In this commentary, we address the following important aspects of LAICOD: (1) the magnitude of the public health problem; (2) the risk of stroke and other cardiovascular diseases associated with intracranial occlusive disease; (3) the etiology; (4) medication and nonmedication approaches to treatment and prevention; and (5) gaps in our understanding of intracranial occlusive disease and possible next steps to unravel enigmas related to this disorder.

Global Burden of Large Artery Intracranial Occlusive Disease

LAICOD has emerged as the most common stroke subtype worldwide as emphasized in a recently published Research Letter in *Stroke*.[11] In a review of the global burden of intracranial atherosclerosis, Wong[12] points out, as has Caplan,[13] for many years that only recently have clinical trials targeted individual stroke subtypes as distinct entities rather than indiscriminately grouping all strokes together as though homogeneous. In relation to atherosclerotic stroke mechanisms, Wong[12] concludes that although extracranial large artery atherosclerosis may be a more common lesion in whites in Europe and America, LAICOD affecting the middle cerebral artery, intracranial portion of the internal carotid artery, vertebrobasilar artery, and posterior and anterior cerebral arteries is more common in Asian patients. In fact, LAICOD is estimated to account for 33% to 50% of stroke and >50% of transient ischemic attack in Chinese populations; it was found in 47% of patients with stroke in Thailand; and it was significant in approximately 48% of patients with stroke in Singapore.[12] In Korea, LAICOD is estimated to cause up to 20% to 25% of strokes (H.J. Bae, personal communication, December 1, 2007). In Japan, LAICOD frequency remains high; however, extracranial carotid artery atherosclerosis in increasing in this population. Because

Received September 28, 2007; final revision received January 16, 2008; accepted January 18, 2008.

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***Stroke* is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.107.505776**

Table. Comparative Frequency of LAICOD in Patients With Stroke

Ethnic Groups	Reported Frequency of LAICOD in Patients With Stroke (%)
Chinese[12]	33–50
Thai[12]	47
Korean[12]	56
South Asians[11]	54
US Whites[15]	1
US Blacks[15]	6
US Hispanics[15]	11

Asians have a high risk for LAICOD, which may be the same situation for persons of Hispanic and African origin,[14] and these populations constitute an overwhelming majority of the world's population, LAICOD is likely the most common vascular lesion worldwide. The Table lists the comparative frequency of LAICOD in patients with stroke from key areas in the world.[11,12,15]

Risk of Stroke and Other Cardiovascular Disease in Large Artery Intracranial Occlusive Disease

LAICOD is associated with a high risk for ischemic stroke. In WASID, the 2-year recurrent ischemic stroke rates were 19.7% in the aspirin treatment group and 17.2% in the warfarin group.[9] This compares with 8% to 12% in aspirin-treated patients and 8% to 14% in warfarin-treated patients in other recurrent stroke prevention trials.[9] In the African American Antiplatelet Stroke Prevention Study (AAASPS), where the predominant stroke subtype at baseline among these very high-risk patients was lacunar infarction (approximately 67%), the fatal plus nonfatal recurrent stroke frequencies were 11.7% for ticlopidine treatment and 9.5% for aspirin treatment.[16] In WASID, predictors of recurrent stroke risk were stenosis ≥70%, recent symptoms (≤17 days), and female sex.[17]

LAICOD may not exist in isolation as a sole atherosclerotic occlusive lesion. Death from myocardial infarction was uncommon in WASID (none in the aspirin treatment group, 3 in the warfarin group), and the occurrence of fatal or nonfatal myocardial infarction was relatively uncommon in WASID (7 in the aspirin group, 12 in the warfarin group) among 280 patients treated with aspirin and 289 patients treated with warfarin.[9] Coronary atherosclerosis, however, may occur in association with LAICOD. The correlation of coronary atherosclerosis in Korean patients, however, may be stronger for extracranial carotid atherosclerosis than LAICOD.[18] Concomitant occurrence of LAICOD and coronary atherosclerosis should not be unexpected because intracranial atherostenosis may be associated with aortic plaque[19] and metabolic syndrome,[20] factors that may be associated with coronary atherosclerosis. The GESICA natural history study based in France suggests both a high 2-year recurrence rate of ischemic events in the stenotic cerebral artery territory (38.2% with stroke accounting for 13.7% and transient ischemic attack 24.5% of events) and cardiovascular events in 18.6% with an 8.8% vascular death rate.[21]

Etiology

Despite the high prevalence and importance of LAICOD, there is a relative paucity of information about causation. Studies from Wong's group in Hong Kong[22,23] and another study[24] suggest a possible role for diabetes mellitus, metabolic syndrome, and other cardiovascular risk factors. Furthermore, several studies have attempted to explain racial differences in the distribution of extracranial and intracranial occlusive disease.[1,2] Hypotheses regarding level of raised blood pressure (predisposing to intracranial occlusive disease) or elevated cholesterol (predisposing to extracranial occlusive disease) have been applied to explain these differences. In the international Extracranial/Intracranial Bypass Trial, race (black, Asian) was associated with lesion distribution in multivariate analysis.[25] In the Northern Manhattan Stroke Study, a greater occurrence of diabetes and hypercholesterolemia was noted among blacks and Hispanics, which accounted for a major proportion of the increased frequency of intracranial occlusive disease.[26]

Caplan has suggested that high blood volume states associated with such factors as female sex (eg, during pregnancy, menstruation), diabetes, and hypertension in blacks and Asians may explain race–ethnic propensity for LAICOD.[26] Burke and Howard provide an interesting alternative perspective on the distribution of asymptomatic extracranial atherosclerosis in blacks and whites whereby population studies suggest at least an equal amount of asymptomatic extracranial atherosclerosis in blacks and whites when measures of intimal media thickness are taken into account.[27] This may be explained, at least in part, by younger age of stroke onset in blacks (ie, full-blown atherosclerosis, which has been studied at referral-based centers, is more prevalent in older age) and different stroke subtypes such as hemorrhagic stroke related to hypertension, which occurs at younger ages in blacks and serves as a competing cause of mortality.

Several interesting observations have been published recently in relation to etiology and pathophysiology of LAICOD. For example, despite the uncertainty about the etiology of LAICOD, embolism and hypoperfusion are important factors in causing recurrent stroke.[28–30] Furthermore, age, hypertension, and diabetes mellitus have been shown to be independent risks for asymptomatic LAICOD.[31]

Approaches to Treatment and Prevention

Overall, treatment and prevention of LAICOD has been unsuccessful. For example, study of a low-molecular-weight heparin, 3800 IU nadroparin calcium antifactor Xa twice daily subcutaneously versus 160 mg oral aspirin daily for 10 days in Asian patients with acute ischemic stroke and predominantly LAICOD has been reported. There was no significant benefit for nadroparin calcium at 6 months on the Barthel index (absolute reduction 4%; 95% CI, −5 to 13), the primary outcome measure.[32] In addition, for recurrent stroke prevention, the WASID study did not show significant efficacy of warfarin over aspirin therapy for LAICOD but showed an excess of hemorrhages.[9] The international Extracranial to Intracranial Bypass Trial suggested that bypass might be deleterious for some intracranial occlusive lesions in nonprimary analysis.[8] Other agents such as cilostazol may hold promise[33] as may antihypertensive agents and cholesterol-lowering drugs, which could merit further large-scale study for first and recurrent stroke prevention. Revascularization and flow augmentation with intracranial stenting and counterpulsation devices continue to be studied in this important field.[10,34]

Intracranial revascularization with the Wingspan stent has been approved by the US Federal Drug Administration for patients with medically refractive LAICOD.

Gaps and Next Steps

LAICOD is a major worldwide stroke problem that we cannot ignore. It seems to be the most common stroke subtype and will likely become an even more important public health problem if the world population expands in developing regions where LAICOD is prevalent. The etiology of LAICOD remains poorly defined. Important but limited epidemiological studies have been undertaken to better understand mechanisms of LAICOD. A more precise elucidation of pathophysiological mechanisms leading to LAICOD would be a major advance in our quest for prevention and treatment of this disorder. LAICOD is subject to progression that is associated with increased risk of cerebrovascular events.[31,35]

It is again time to consider pooling our collective knowledge to form international collaborations to better study and define LAICOD so that we can develop new therapies and better use existent medications and devices to treat and prevent LAICOD.[2] International epidemiological efforts may take the form of hypothesis-driven collaborative registries for LAICOD and population- or cohort-based regional comparisons to better understand risk factors. This comparative approach may focus on the possible role of traditional cardiovascular risk factors, genetic factors, and other potential novel factors in conferring risk of first and recurrent stroke. In addition, international collaborative clinical trials should be considered or continued to test medications that control risk factors suspected of causing LAICOD and devices that may improve risk of first or recurrent stroke in conjunction with LAICOD. Because the intracranial and extracranial arteries differ structurally, there may be opportunities for basic studies to open up new avenues for treatment and prevention.[26] A collaborative international basic science approach is warranted to elucidate new mechanisms to target for prevention and treatment of LAICOD, a disorder that is far reaching worldwide.[36]

Disclosures

P.B.G. serves on the Steering Committees for PRoFESS (Boehringer Ingelheim), ARRIVE (Bayer), Pharm-D and Brainsgate; Data Safety and Monitoring Board for Statistical Collaboration, Inc (Merck study); Adjudication Committees for TAP and Myriad; Safety Committee for Novartis (Aliskiren); Consultant to Boehringer Ingelheim, Daiichi-Sankyo, and Takeda; and Speaker's Bureau for Boehringer Ingelheim. The remaining authors report no conflicts.

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