Risk Factors, Regional Disparity and Trends of Ischemic Stroke Etiologic Subtypes

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Introduction

Stroke remains the leading cause of morbidity and mortality in the world. Unlike coronary heart disease, stroke can occur due to different etiologies, and the pathogenesis, treatment, and prognosis can vary. There are different etiological classification systems: most articles used the Trial of Org 10172 in Acute Stroke Treatment classification system, but articles using other classification systems have been noted.[1] Despite differences in details among the classification systems, large artery atherosclerosis (LAA), small-vessel disease (SVD), and cardioembolism (CE) were the most frequently analyzed subtypes due to their high proportions among patients, their high number of known risk factors, and the fact that some of the risk factors were controllable. The proportions of subtypes were different among regions. In a systematic review comparing the epidemiology of stroke and its subtypes, the proportion of SVD strokes was higher in Chinese than in Caucasian whether in hospital- or community-based studies.[2] In addition, the proportion of subtypes might change with time, as a result of industrial improvement and medical prevention. Analyzing the trend in subtypes is of vital importance for judging the effect of prevention procedures and providing advice for subsequent steps.

Risk Factors for Specific Subtypes

LAA stroke refers to patients with significant stenosis or occlusion of a major brain artery or branch cortical artery. Low-density lipoprotein cholesterol (LDL-C) is critical in the progression of atherosclerosis.[3,4] It has been regarded as a preventive target in consensus guidelines (<1.8 mmol/L is the target).[5] The Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound study showed that a lower level of LDL-C was correlated with greater regression of coronary plaque.[6] Comparison of the risk factors between the LAA and SVD subtypes showed that LDL-C was more strongly related to the LAA

subtype.[7] Spence and Solo[8] have recently reported that some atherosclerosis plaques could be regressed by lowering LDL-C, but others could not be regressed by this method alone. Age, impaired renal function, and other unknown factors also contributed to the process. Statins are an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase, which can reduce the LDL-C level. One of the cornerstone achievements in preventing stroke events in the past decade was the use of statins, first described by the Stroke Prevention with Aggressive Reduction in Cholesterol Levels study.[9] In 2008 and 2011, the American Heart Association/American Stroke Association consecutively published guidelines to recommend using statins for secondary and primary stroke prevention.[5,10] Based on the above, changes in medical practice could make a difference in LAA stroke distribution.

CE strokes account for another portion of overall ischemic strokes. The risk factors are atrial fibrillation (AF), systolic heart failure, recent myocardial infarction, patent foramen ovale (PFO), and others.[11] AF is the most common condition. Studies have shown AF to be correlated with a 2–7 times higher risk of stroke.[12] The prevalence of AF increases markedly with age. It changes sharply from 0.1% among adults aged <55 years to almost 10% among adults aged >80 years.[13] As aging of the population becomes a worldwide phenomenon, it has been predicted that the number of patients with AF may double and the number of AF-related strokes may triple in the next few decades.[13] Some cases of AF present as a single episode and go undetected by 12-lead electrocardiogram, also called paroxysmal AF, which should also be emphasized. It was found that patients with paroxysmal AF lasting ≥6 min during the first 3 months after device implantation experienced a

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2.5-time higher risk of stroke during an average 2.5 years of follow-up.[14] Prolonged use of the detection device could increase the positive findings. The Cryptogenic Stroke and Underlying AF trial demonstrated that in patients with insertable cardiac monitors, the sensitivity of AF diagnosis was lowest with a 24-h Holter monitor (1.3%) and highest with a 30-day event recorder (22.8%) for a single monitoring period.[15] Once a cardioembolic source is confirmed for a stroke patient, anticoagulation treatment should be started.[5] Warfarin is a classical anticoagulant drug, which requires frequent monitoring and significantly increases the risk of hemorrhagic events, including intracranial hemorrhage. The new oral anticoagulants have a stable effect with a faster onset of action and do not require monitoring, offering a new choice for stroke prevention in AF patients.[16]

The SVD subtype, also called lacuna stroke, usually occurs due to the fibrinoid necrosis and lipohyalinosis of arterioles affected by hypertension-induced pathological processes. In addition to its influence on stroke occurrence, hypertension is also specifically related to recurrent strokes in patients with SVD strokes but not other subtypes of stroke. Russell was the first to propose that lowering hypertension could reduce the rate of SVD stroke. In the later Perindopril Protection Against Recurrent Stroke (PROGRESS) study, the risk of initial stroke was reduced by almost one-quarter with active antihypertensive treatment.[17] However, hypertension awareness and control varied among different regions. Based on previous community studies, the prevalence of hypertension was 29.6% and the control rate 9.3% in China as of 2014, which was lower than those in some developed countries, such as America (29.3% and 36.8% in 2004, respectively).[18]

Other known etiologies of stroke include hypercoagulable states, nonatherosclerotic vasculopathies and so on. These etiologies are generally uncommon, and their proportions are influenced by the presence of other etiological subtypes.[1]

Despite both common and uncommon known etiologies in stroke patients, the etiology remained undetectable after comprehensive evaluations in some stroke patients (UE stroke). Ascertaining the etiology of stroke patients is important for a clinical physician because further secondary prevention might be affected (antiplatelet or anticoagulation). The situation could be different in developed and developing countries. Economic status influences both medical resources and the affordability of medicine to patients, and the arrangements for detecting etiology might be different. Advanced techniques have been useful in reducing the number of UE strokes: prolonged electrocardiograph monitoring is a good example of this phenomenon, as previously discussed.

DISTRIBUTION OF ISCHEMIC STROKE SUBTYPES IN DIFFERENT REGIONS

The distributions of ischemic stroke (IS) subtypes were different among different regions. Asian and African stroke patients featured a higher proportion of SVD subtypes.[2] In North American and European studies, regional and ethnic variations exist.[19] The influencing factors are multiple and complicated. First, genetic differences exist among different ethnicities. It has been reported that genetic factors contribute up to 30–40% of stroke risk. In addition, genome-wide association studies have identified a number of genetic associations specific to individual subtypes.[20] Second, conventional risk factors play an important role in IS subtype distribution, which is influenced by lifestyle and economic status.

WORLDWIDE TRENDS IN ISCHEMIC STROKE SUBTYPES IN DIFFERENT COUNTRIES

We searched the database for studies investigating trends in stroke etiology in different countries. Research in Canada showed declines in the LAA subtype and the SVD subtype associated with declines in LDL-C and blood pressure. The CE subtype increased significantly, with the greatest increase in PFO, but AF did not.[19] Research in Korea reported an increase in the CE subtype, a decrease in the SVD subtype, and stable levels of the LAA subtype.[21] Research in Poland showed that the LAA subtype increased, as did the CE subtype, while the SVD subtype decreased significantly in 1995–2013.[22] Research in Australia revealed an increase of 1.4 times in AF-related stroke and transient ischemic attack.[23] In a community-based study in Japan, the ischemic stroke subtypes were classified into lacunar, cardioembolic, nonlacunar infarctions, and unclassifiable infarction. It was found that except for nonlacunar infarction, which showed a decreasing trend, the changes in other subtypes were not significant.[24] Since it did not report change of risk factor in the Japanese research, hospital-based studies were mainly compared and discussed.

In general, there was a uniform increasing trend in CE stroke and a decreasing trend in SVD stroke in Canada, Korea, and Poland, but the situation was different for LAA stroke. The trend in ODE stroke is less concerning due to its lower proportion and its uncommon etiologies. The trend in UE stroke was stable in previous articles. The changing trend was influenced by individual lifestyles, risk factors, and etiology diagnostic techniques. First, with economic development, people in some developing countries have transitioned into more western lifestyles, which are characterized by a high proportion of dietary fat and cholesterol. Blood cholesterol levels might become elevated and therefore prone to lead to atherosclerosis.[25] Second, the use of statins and antihypertension drugs is associated with control of the LAA and SVD subtypes of stroke. However, as statins are widely used in China, they may be useful in preventing LAA stroke nationwide. The use of antihypertension medications might not be as strong as it should be, resulting in less control of SVD stroke. Third, etiology diagnostic techniques might be insufficient in some developing countries, including China, which would influence the proportion of UE strokes. Economic

status and emphasis were the two main factors. In regions undergoing rapid economic development, such as China, these items might have increased greatly during the past decade. New techniques to identify the cause of stroke are also influenced by socioeconomic status and by the emphasis of physicians. For example, when paroxysmal AF detection was emphasized, more AF was detected in Korea and Poland, resulting in an increase in the CE subtype.

In summary, with the better control of vascular risk factors in high-income countries, LAA and SVD stroke have begun to show a downtrend. However, in some less developed countries, antihypertension measurements might need to be strengthened. CE stroke continued to increase with the high emphasis on detecting AF, although anticoagulation drug use remains insufficient. The socioeconomic status of the patient is associated with the ability to accomplish the common etiology investigations and might influence the rate of UE strokes, especially in low- or middle-income countries. Combined with the aforementioned issues, it is important to analyze the IS etiology trend in our country, which will be helpful in evaluating the control of risk factors and giving advice on future stroke prevention.

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