Risk Factors Influencing Recurrence of Large Artery Atherosclerotic Cerebral Infarction: Postprint

Authors: Dai Yingyi, Huang Zhixin 2, Liu Xintong, Wang Qizhang 3

Date: 2018-06-15T00:00:00+00:00

Abstract

Objective: To investigate the risk factors for recurrence in patients with first-ever large-artery atherosclerotic cerebral infarction. Methods: Patients with first-ever ischemic stroke who presented to the neurology department were consecutively enrolled and confirmed as large-artery atherosclerotic cerebral infarction by CTA or MRA. All enrolled patients underwent 1-year follow-up and were divided into ischemic stroke recurrence group and non-recurrence group based on whether cerebral infarction recurred during follow-up. Clinical data of the two groups were compared, and independent predictors of recurrent ischemic stroke were identified through univariate analysis and Cox regression model. Results: Two hundred fifty-six patients met the inclusion criteria, and all completed follow-up. Thirty patients (11.7%) developed ischemic cerebrovascular events during follow-up. Univariate analysis showed that differences between the recurrence and non-recurrence groups were statistically significant in terms of drinking habits (P=0.028), smoking (P=0.007), high-density lipoprotein cholesterol (P=0.045), ischemic heart disease (P=0.002), antihypertensive drug use (P=0.036), and statin use (P=0.016). Cox regression analysis showed that irregular statin use (HR=0.410, P=0.043), smoking (HR=2.253, P=0.043), high-density lipoprotein cholesterol (HR=0.327, P=0.029), and ischemic heart disease (HR=8.566, P<0.001) were associated with ischemic stroke recurrence. Conclusion: Irregular statin use, low high-density lipoprotein level, smoking, and prior coronary heart disease are associated with a higher risk of ischemic stroke recurrence.

Full Text

Preamble

Risk Factors for Recurrence of Large Atherosclerotic Cerebral Infarction

Yingyi Dai[1,2], Zhixin Huang[2], Xintong Liu[1,2], Qizhang Wang[3]
[1]Southern Medical University, Guangzhou 510515, China
[2]Department of Neurology, Guangdong Second Provincial General Hospital, Guangzhou 510317, China
[3]Shenzhen Shajing Hospital Affiliated to Guangzhou Medical University, Shenzhen 518104, China

Abstract

Objective To investigate the risk factors for recurrence in patients with first-episode large atherosclerotic cerebral infarction.

Methods We consecutively enrolled first-episode ischemic stroke patients in the neurology department who were confirmed to have large atherosclerotic cerebral infarction by CTA or MRA. All enrolled patients were followed up for one year and divided into recurrent ischemic stroke group and non-recurrent group based on whether cerebral infarction recurred during follow-up. Clinical data between the two groups were compared, and independent predictors of recurrent ischemic stroke were identified through univariate analysis and Cox regression modeling.

Results A total of 256 patients met the inclusion criteria and completed follow-up. Thirty patients (11.7%) experienced ischemic cerebrovascular events during follow-up. Univariate analysis revealed statistically significant differences between recurrent and non-recurrent groups in alcohol consumption (P=0.028), smoking (P=0.007), high-density lipoprotein cholesterol (P=0.045), ischemic heart disease (P=0.002), antihypertensive medication use (P=0.036), and statin use (P=0.016). Cox regression analysis showed that irregular statin use (HR=0.410, P=0.043), smoking (HR=2.253, P=0.043), high-density lipoprotein cholesterol (HR=0.327, P=0.029), and ischemic heart disease (HR=8.566, P<0.001) were associated with ischemic stroke recurrence.

Conclusion Patients with first-episode large atherosclerotic cerebral infarction who have irregular statin use, low high-density lipoprotein levels, smoking habit, and history of coronary heart disease are at higher risk for stroke recurrence.

Keywords: cerebral infarction; recurrent stroke; risk factor

Introduction

Epidemiological surveys indicate that in China, one person experiences a stroke every 12 seconds, and one person dies from stroke every 21 seconds, with approximately 2.7 million new cerebrovascular disease cases annually—a trend that

continues to rise, particularly in rural areas. While incidence rates are lower in Western countries, stroke remains a major health concern; for instance, in the United States, one person suffers a stroke every 40 seconds, with ischemic stroke accounting for 87% of cases [**?**]. Ischemic stroke carries a high recurrence rate, with previous studies from Western stroke registries reporting cumulative recurrence rates of 17-30% within five years post-stroke [**?**]. Although ischemic stroke has multiple etiologies and risk factors, atherosclerosis represents the primary pathogenic factor, especially in populations over 50 years old [**?**]. Rupture of unstable plaques in progressive atherosclerosis can lead to artery-to-artery embolism, while atherosclerotic occlusion or severe stenosis without effective collateral circulation may cause cerebral hypoperfusion and even infarction. Atherosclerosis can affect both extracranial and intracranial large arteries as well as smaller perforating arteries, with small artery atherosclerotic disease potentially causing lacunar infarction. Cardioembolic ischemic stroke most commonly occurs in atrial fibrillation patients and is often an indirect consequence of ischemic heart disease secondary to atherosclerosis.

In the latest Chinese ischemic stroke subtype classification, large artery atherosclerotic stroke represents a common clinical type of cerebral infarction characterized by severe clinical symptoms, poor prognosis, and high recurrence rates [**?**]. Compared with intracranial medium and small arteries, large arteries possess richer lipid intimal structures. When macrophages migrating beneath the intima ingest large amounts of lipids, they evolve into foam cells. Massive deposition of foam cells in the vascular wall forms atherosclerotic plaques, increasing vessel wall fragility, causing stenosis, and creating unstable plaques, which significantly elevate the risk of ischemic stroke occurrence and recurrence [**?**]. Therefore, intervention on potential risk factors associated with large artery atherosclerotic vascular disease is crucial in treating ischemic cerebrovascular disease and preventing recurrence [**?**]. Current research has identified numerous risk factors for large artery atherosclerotic stroke. For example, Wang et al. [**?**] analyzed risk factors and distribution characteristics of first-episode acute ischemic stroke due to large artery atherosclerosis, identifying metabolic syndrome and apolipoprotein B/apolipoprotein A1 ratio changes as factors associated with intracranial atherosclerotic stenosis, with differences in risk factors for first cerebral infarction between anterior and posterior circulations —posterior circulation infarction showing closer association with metabolic disorder-related indicators. Zhang et al. [**?**] compared risk factors between large artery atherosclerotic stenotic cerebral infarction and small artery occlusive cerebral infarction, finding diabetes and age as independent risk factors for large artery atherosclerotic stenotic cerebral infarction. Duan et al. [**?**] analyzed risk factors for leukoaraiosis in large artery atherosclerosis patients, identifying age, hypertension, diabetes, and number of stenotic or occluded arteries as high-risk factors. Neurological impairment in large artery atherosclerotic stroke is often associated with hypertension, neurological status at admission, and the degree and number of vascular stenoses on imaging [**?**]. Additionally, research has observed the effect of statin pretreatment on microemboli formation in

large artery atherosclerotic stroke, finding that statins can dose-dependently reduce microemboli formation [**?**]. While many studies have reported analysis of risk factors for large artery atherosclerotic stroke, most have focused on first-episode stroke and clinical prognosis, with few evaluating risk factors for recurrent stroke. Therefore, this study analyzes potential risk factors affecting recurrence of large artery atherosclerotic cerebral infarction to provide scientific basis for further preventive interventions.

1.1 Clinical Data

Inclusion criteria: Diagnosis of ischemic stroke according to the cerebrovascular disease classification issued at the 4th National Cerebrovascular Disease Conference; age 18 years; onset time $<$ 7 days; complete imaging data confirming presence of ischemic lesions.

Exclusion criteria: (1) Within thrombolysis time window; (2) Intracerebral hemorrhage indicated by CT; (3) History of carotid endarterectomy or carotid stenting; (4) History of previous ischemic stroke; (5) Severe cardiac, hepatic, or renal insufficiency.

We consecutively enrolled 256 patients with first-episode acute ischemic stroke admitted to our hospital between December 2012 and January 2014, with etiological classification considered as large artery atherosclerosis type [**?**]. The cohort comprised 178 males and 78 females with mean age 62$\pm$12 years. All patients were admitted within 7 days of onset and confirmed to have cerebral infarction by CT and MR diffusion sequences. Stroke severity was assessed using the National Institutes of Health Stroke Scale. A research nurse (blinded to imaging data) collected admission data, demographic information, medical history, and complete examination results within 7 days of admission. The endpoint event was first ischemic stroke recurrence within half a year, defined as new neurological deficit symptoms lasting at least 24 hours (confirmed by CT/MR). The 256 enrolled patients were divided into ischemic stroke recurrent group and non-recurrent group based on whether the endpoint event occurred. This study was approved by the hospital ethics committee, and all patients or their families provided informed consent.

1.2 Statistical Analysis

SPSS 18.0 statistical software was used. Clinical data at admission were compared between groups, including gender, age, glycated hemoglobin, blood lipids (triglycerides, total cholesterol, high-density lipoprotein, low-density lipoprotein), homocysteine, comorbidities (hypertension, diabetes, hyperlipidemia, coronary heart disease), smoking history, alcohol consumption, continuous use of antiplatelet/lipid-lowering/antihypertensive/diabetes medications, participation in housework, and sleep quality.

Independent samples t-test was used for intergroup comparisons, Kruskal-Wallis or Mann-Whitney U test for non-normally distributed continuous variables, and

chi-square or Fisher' s test for categorical variables. Variables with P<0.2 in univariate analysis were included in the Cox regression model (Enter method) to identify factors influencing stroke recurrence in patients with acute large artery atherosclerotic cerebral infarction, with P<0.05 considered statistically significant.

Among 256 acute ischemic stroke patients, 30 (11.7%) experienced recurrence (recurrent cerebral infarction group). This group had a mean age of 60 years, including 22 male patients (73.3%), 24 hypertensive patients (80.0%), 14 diabetic patients (46.7%), 16 smokers (53.3%), and 5 patients with coronary atherosclerotic heart disease (16.7%). Comparison of clinical data between groups is shown in Table 1 . Univariate analysis indicated that the recurrent group had higher proportions of smoking, alcohol consumption, and coronary atherosclerotic heart disease, but lower proportions of statin and antihypertensive medication use compared with the non-recurrent group (P<0.05). Variables with P<0.2 included age, total cholesterol, high-density lipoprotein, low-density lipoprotein, alcohol consumption, smoking, statin and antihypertensive medication use, housework, and coronary heart disease. Cox regression analysis revealed that history of coronary heart disease (HR=8.566, 95% CI 2.866-25.600, P<0.001), high-density lipoprotein level (HR=0.327, 95% CI 0.120-0.893, P=0.029), smoking (HR=2.253, 95% CI 1.026-4.951, P=0.043), and statin therapy (HR=0.410, 95% CI 0.180-0.937, P=0.034) were independent predictors of recurrent ischemic stroke (Table 2).

Discussion

Classic risk factors for ischemic stroke recurrence include cardiac disease, hypertension, diabetes, smoking, and lipid metabolism disorders [**?**], which target all vascular lesions. However, few studies have focused on risk factors specifically for large vessel disease. This study analyzed risk factors for recurrence of large artery atherosclerotic cerebral infarction, demonstrating that the main high-risk factors for recurrence were history of coronary heart disease, high-density lipoprotein level, smoking, and irregular statin therapy. Compared with classic risk factors, heart disease, lipid metabolism, and smoking are common factors, whereas diabetes was not an independent risk factor for large artery atherosclerotic stroke recurrence. The possible reason is that persistent hyperglycemia and macromolecular proteins in diabetic blood form irreversible advanced glycation end products under non-enzymatic conditions, which mainly deposit in medium and small vessel walls, causing lesions primarily in medium and small vessels [**?**]. However, the exact mechanism requires further investigation.

Coronary atherosclerotic heart disease (coronary heart disease) and ischemic cerebral infarction share similar etiology and atherosclerotic pathogenesis. Multiple studies have found an increased proportion of coronary heart disease in patients with recurrent ischemic cerebral infarction, consistent with our findings, leading to coronary heart disease being considered an independent risk factor for recurrent ischemic cerebral infarction [**?**]. Research indicates that re-

current ischemic stroke is predominantly large artery atherosclerotic type. In patients with severe symptomatic internal carotid artery stenosis, microembolic signals detected by transcranial Doppler remain significantly associated with recurrent ischemic stroke after adjusting for stroke risk factors, highlighting the important role of unstable plaques in stroke recurrence [**?**].

Previous studies have shown that patients with higher high-density lipoprotein levels have relatively lower risk of coronary heart disease [**?**], and increasing high-density lipoprotein can reduce the incidence of coronary events [**?**]. Compared with first-episode ischemic stroke, low-density lipoprotein level is more closely associated with large artery atherosclerotic cerebral infarction recurrence [**?**]. In recent years, accumulating evidence has demonstrated that dyslipidemia, particularly high-density and low-density lipoprotein cholesterol, plays an important role in the pathogenesis of vascular atherosclerosis [**?**]. Multiple studies also support that dyslipidemia has greater impact on occlusive large artery atherosclerotic disease [**?**].

Furthermore, our results showed that irregular statin use was significantly more common in the recurrent group than in the non-recurrent group. Cox regression analysis also indicated that irregular statin use was closely associated with stroke recurrence and represented an important factor affecting prognosis in this patient cohort. Long-term statin therapy can reduce progression of recurrent stroke, delay atherosclerosis, and even decrease the degree of atherosclerotic stenosis [**?**].

Regarding lifestyle factors, unhealthy lifestyles such as smoking, alcohol consumption, obesity, and lack of physical exercise show positive correlation with ischemic stroke recurrence, particularly among young and middle-aged patients with acute ischemic cerebral infarction who often exhibit these unhealthy behaviors [**?**]. The harm lies in that long-term unhealthy lifestyle habits are often accompanied by metabolic syndrome and hyperuricemia, which activate inflammatory responses, cause secondary vasomotor dysfunction, coagulation abnormalities, and stimulate the RAS system, thereby leading to atherosclerosis, coronary heart disease, and stroke recurrence [**?**]. Although different ethnic groups show varying sensitivity to smoking [**?**], it is well-established that smoking represents one of the important risk factors for cerebrovascular disease [**?**]. However, few reports have examined whether smoking affects ischemic stroke recurrence. Our cohort study found that smoking was closely associated with ischemic stroke recurrence even after adjusting for other traditional risk factors. A few previous studies have also indicated that smoking correlates with recurrence of large artery atherosclerotic ischemic stroke [**?**, **?**]. Therefore, health education on healthy lifestyle should be strengthened for post-stroke patients to reduce stroke recurrence.

In summary, standardized secondary prevention pharmacotherapy should emphasize etiological control and maintenance of healthy lifestyle. Individualized treatment plans should be developed for patients with ischemic cerebrovascular disease based on etiology and pathogenesis, while health education should be

enhanced to help patients establish reasonable lifestyles, quit smoking and alcohol, maintain proper diet, engage in regular appropriate exercise, and maintain good habits.

References

[?] Roger VL, Go AS, Lloyd DM, et al. Heart disease and stroke statistics-2012 update: a report from the American Heart Association. Circulation, 2012, 125(1): e218-20.

[?] Petty GW, Brown RD, Whisnant JP, et al. Ischemic stroke subtypes: a population-based study of functional outcome, survival, and recurrence. Stroke, 2000, 31(5): 1062-8.

[?] Saber H, Thrift AG, Kapral MK, et al. Incidence, recurrence, and long-term survival of ischemic stroke subtypes: a population-based study in the Middle East. Int J Stroke, 2017, 12(8): 835-43.

[?] Zinkstok SM, Beenen LF, Majoie CB, et al. Early deterioration after thrombolysis plus aspirin in acute stroke: a post hoc analysis of the antiplatelet therapy in combination with recombinant t-PA thrombolysis in ischemic stroke trial. Stroke, 2014, 45(10): 3080-

[?] Chinese Stroke Association Science Statement Expert Group. Management standards for symptomatic intracranial and extracranial atherosclerotic large artery stenosis—Chinese Stroke Association Science Statement. Chinese Journal of Stroke, 2017, 27(1): 64-71.

[?] Moore KJ, Sheedy FJ, Fisher EA. Macrophages in atherosclerosis: a dynamic balance. Nat Rev Immunol, 2013, 13(10): 709-21.

[?] Kolodgie FD, Yahagi K, Mori H, et al. High-risk carotid plaque: lessons learned from histopathology. Semin Vasc Surg, 2017, 30(1): 31-43.

[?] Kim YD, Song D, Nam HS, et al. Increased risk of cardiovascular events in stroke patients who had not undergone evaluation for coronary artery disease. Yonsei Med J, 2017, 58(1): 114-22.

[?] Wang YQ, Sun SY, Zhang BJ, et al. Risk factors and distribution characteristics of large artery atherosclerotic first-episode acute ischemic stroke. Chinese Journal of Nervous and Mental Diseases, 2016, 42(4):

[?] Zhang GB, Yu K, Ji RJ, et al. Analysis of risk factors for large artery atherosclerotic stenotic cerebral infarction. Clinical Focus, 2016, 31(1): 77-80.

[?] Duan ZP, Dai CB, Zhang YH, et al. Analysis of risk factors for leukoaraiosis in patients with large artery atherosclerotic stroke. Chinese Journal of Cerebrovascular Diseases, 2014, 11(9): 449-53.

[?] Yamamoto N, Satomi J, Yamamoto Y, et al. Risk factors of neurological deterioration in patients with cerebral infarction due to Large-Artery atherosclerosis.

J Stroke Cerebrovasc Dis, 2017, 26(8): 1801-6.

[?] Safouris A, Krogias C, Sharma VK, et al. Statin pretreatment and microembolic signals in large artery atherosclerosis. Arterioscler Thromb Vasc Biol, 2017, 37(7): 1415-22.

[?] Adams HP, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke, definitions for use in a multicenter clinical trial. Stroke, 1993, 24(1): 35-41.

[?] Esenwa C, Gutierrez J. Secondary stroke prevention: challenges and solutions. Vasc Health Risk Manag, 2015, 11(11): 437-50.

[?] Walcher D, Marx N. Advanced glycation end products and C-peptide-modulators in diabetic vasculopathy and atherogenesis. Semin Immunopathol, 2009, 31(1): 103-11.

[?] Elmariah S, Furlan AJ, Reisman M, et al. Predictors of recurrent events in patients with cryptogenic stroke and patent foramen ovale within the CLOSURE I (Evaluation of the STARFlex Septal Closure System in Patients With a Stroke and/or Transient Ischemic Attack Due to Presumed Paradoxical Embolism Through a Patent Foramen Ovale) trial. JACC Cardiovasc Interv, 2014, 7(8): 913-

[?] Fu J, Tang J, Yang J, et al. Adding computed tomography and transcranial doppler findings to the ABCD2 score to predict long-term risk of stroke after transient ischaemic attack or minor stroke. Eur J Neurol, 2015, 22(3): 520-6.

[?] Ito T, Arima H, Fujiyoshi A, et al. Relationship between non-high-density lipoprotein cholesterol and the long-term mortality of cardiovascular diseases: Nippon Data 90. Int J Cardiol, 2016, 220(19): 262-7.

[?] HPS3/TIMI55-REVEAL Collaborative Group, Bowman L, Hopewell JC, et al. Effects of anacetrapib in patients with atherosclerotic vascular disease. N Engl J Med, 2017, 377(13): 1217-27.

[?] Stekkinger E, Scholten R, van der Vlugt MJ, et al. Metabolic syndrome and the risk for recurrent pre-eclampsia: a retrospective cohort study. BJOG, 2013, 120(8): 979-86.

[?] Andrews AM, Muzorewa TT, Zaccheo KA, et al. Cholesterol enrichment impairs capacitative calcium entry, eNOS phosphorylation & shear stress-induced NO production. Cell Mol Bioeng, 2017, 10(1): 30-40.

[?] Wang IK, Liu CH, Yen TH, et al. Cholesterol levels are associated with 30-day mortality from ischemic stroke in dialysis patients. J Stroke Cerebrovasc Dis, 2017, 26(6): 1349-56.

[?] Chou R, Dana T, Blazina I, et al. Statins for prevention of cardiovascular disease in adults: evidence report and systematic review for the US preventive services task force. JAMA, 2016, 316(19): 2008-24.

[?] Lee PN, Thornton AJ, Forey BA, et al. Environmental tobacco smoke exposure and risk of stroke in never smokers: an updated review with Meta-Analysis. J Stroke Cerebrovasc Dis, 2017, 26(1): 204-16.

[?] Lin MP, Ovbiagele B, Markovic D, et al. Association of secondhand smoke with stroke outcomes. Stroke, 2016, 47(11): 2828-35.

[?] Deijle IA, Van Schaik SM, Van Wegen EE, et al. Lifestyle interventions to prevent cardiovascular events after stroke and transient ischemic attack: systematic review and Meta-Analysis. Stroke, 2017, 48(1): 174-9.

[?] O' neal WT, Judd SE, Limdi NA, et al. Differential impact of risk factors in blacks and whites in the development of atrial fibrillation: the reasons for geographic and racial differences in stroke (REGARDS) study. J Racial Ethn Health Disparities, 2017, 4(4):

[?] Fukui S, Imazeki R, Amano Y, et al. Common and specific risk factors for ischemic stroke in elderly: Differences based on type of ischemic stroke and aging. J Neurol Sci, 2017, 380(9): 85-91.

[?] Kaisar MA, Villalba H, Prasad S, et al. Offsetting the impact of smoking and e-cigarette vaping on the cerebrovascular system and stroke injury: Is Metformin a viable countermeasure? Redox Biol, 2017, 13(6): 353-62.

[?] Feng SJ, Liu M, Li WZ, et al. Study on recurrence and influencing factors in stroke patients. Journal of Southern Medical University, 2009, 29(5): 983-5.

Note: Figure translations are in progress. See original paper for figures.