ATHEROECLEROSIS RISK FACTORS AND ETIOLOGIC MECHANISMS OF LACUNAR STROKE

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Abstract

INTRODUCTION: It is thought that lacunae occur in patients with hypertension or diabetes mellitus as small-vessel involvement. The frequency of other stroke mechanisms in patients with lacune was evaluated in this study.

METHODS: Consecutive stroke patients admitted to Valie-Asr Hospital, Khorasan in 2006 were enrolled in a prospective study. Diagnosis of stroke and its risk factors was made by a stroke neurologist. All of the stroke patients underwent a standard battery of diagnostic investigations. Brain infarction was categorized as lacune and large-vessel territory infarction (LVTI). Chi-square test and odds ratios were used for statistical analysis.

RESULTS: Ninety-six patients with lacune and 252 patients with LVTI were studied. The frequency of diabetes and hypercholesterolemia was significantly higher in patients with lacunar stroke than in those with LVTI (P=0.034, P<0.001 respectively). The frequency of hypertension, smoking, TIA and ipsilateral carotid stenosis was not significantly different between the two groups (P=0.94, P=0.59, P=0.37, P=0.13, respectively). Atrial fibrillation was significantly more frequent in patients with LVTI (P<0.001). The frequency of various etiologic mechanisms was not significantly different in lacunar and LVTI patients (df=4, P=0.164).

CONCLUSIONS: Hypertension in patients with lacune is not more frequent than other stroke patients. Cardioembolism and artery to artery embolism are important but less common mechanisms of lacunae.

Keywords: Atherosclerosis, lacune, stroke.


Introduction

About one-quarter of all ischemic strokes and transient ischemic attacks (TIA) are lacunar.1 Lacunae are small, deep infarcts that occur in the subcortical regions of the brain, including the deep white matter, basal ganglia, internal capsule, thalamus and brain stem. Lacunae occur in association with occlusion of deep penetrating arterioles.1 Small vessel lipohyalinosis or microatheroma formation is the usual underlying pathologic lesion.1 Hypertension and diabetes mellitus have been reported as the most frequent risk factors associated with the development of lipohyalinosis and subsequent lacunar infarction.1,2 These risk factors are not present in all cases and pathologic investigation of lacunae has not always confirmed the presence of small-vessel disease.2 The true risk factor profile for lacunar infarction is still being developed.3 Despite the availability of effective antihypertensive medications, the incidence of lacunar stroke has not changed in recent decades.3 Thus, the influence of hypertension as a lacunar risk factor is attenuated. Other etiologies of lacunar infarctions include intracranial atherosclerotic disease and embolism from carotid lesions or the heart.2 Neurocysticercosis, neuroborreliosis and acquired immunodeficiency syndrome affecting small arteries can produce lacunar infarcts.4 Coexistence of multiple etiologies in some patients with lacunar infarction obscures the determination of a precise cause.4 Microemboli might be the cause of an important minority of lacunar events1. The issue is of key importance when an ipsilateral carotid stenosis is considered as lacunar stroke etiology and makes the patient a candidate for carotid endarterectomy. Genetic susceptibility determines which patients with hypertension and diabetes will develop lacunar infarcts or large-vessel atherosclerosis and cortical infarction.5 However, many patients have different ischemic stroke subtypes at different times.5 This study was designed to compare the prevalence of risk factors and etiologies in patients with lacunar and non-lacunar infarcts.

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Materials and methods
Consecutive patients with brain infarction admitted to Valie-Asr Hospital, Khorasan in 2006 were enrolled in a prospective study. Stroke was defined as an ischemic focal neurological deficit persisting at least 24 hours. The diagnostic and etiologic investigations of stroke were made by a stroke neurologist. All of the patients underwent a standard battery of diagnostic investigations, including brain CT, ECG, blood electrolytes, blood count and differential, coagulation profile, fasting blood sugar and lipid profile, duplex sonography of supra-aortic trunks, transcranial Doppler and transthoracic echocardiography. 24-hour Holter monitoring was performed in patients with history of syncope and/or palpitation with non-diagnostic ECG. Transesophageal echocardiography was performed in cases with non-diagnostic transthoracic echocardiography despite high suspicion of cardioembolism. Brain MRI/MRA was performed in suspected arterial dissection, arteriovenous malformation or aneurysm. Patients with normal initial brain CT scan underwent a second scan 48 hours after stroke.

Sequential axial slices, 5 mm in thickness, were acquired. TIA was defined as sudden-onset ischemic focal neurologic deficit lasting less than twenty four hours. Etiologic and topographic diagnosis were made using Practical Iranian Criteria (PIC) for classification of brain infarction. Atherosclerosis is defined based on the PIC with consideration of vascular risk factors and corresponding arterial stenosis. Traditional lacunar syndromes included pure motor hemiparesis, pure sensory deficit, sensorimotor syndrome, ataxic hemiparesis and dysarthria-clumsy hand syndrome. Patients with lacunar syndrome and normal CT/MRI or a relevant subcortical or brain stem lesion less than 2 centimeters in diameter were considered as cases of lacunar stroke. LVITI consisted of cortical infarcts or subcortical infarcts greater than 2 cm in diameter. Hypertension was defined as using antihypertensive medications or having two blood pressure readings (at least 1 week apart) of >140/90 mm/Hg. Administration of antidiabetic medications or fasting blood glucose >6.4 mmol/L or >126 mg/dL were considered as the definitions of diabetes mellitus. Hypercholesterolemia was defined as use of lipid-lowering medications or fasting cholesterol >5.2 mmol/L or >200 mg/dL. Fasting blood sugar and lipid profile were part of the routine investigations performed within the first 48 hours of stroke. Patients who smoked more than 5 cigarettes per day in recent years were defined as smokers. Patients with head trauma, primary intracerebral hemorrhage and subarachnoid hemorrhage were excluded. Data on the patients’ demographics, clinical presentation and results of investigations were entered in SPSS 9 software package. Chi-square test and odds ratio were used for statistical analysis and P >0.05 was considered as significant.

Results
Ninety-six patients with lacunae (52 females, 44 males) and 252 patients with LVTI (132 females, 120 males) were evaluated.
The effect of gender on the frequency of lacunae versus LVTI was not significant \((df=1, P=0.70)\). The mean and standard deviation (SD) of age in patients with lacunae versus LVTI were 66.78±13.91 and 66.53±15.02, respectively, which shows an insignificant difference \((t=0.15, df=339, P=0.88)\).

Figure 1 represents the frequency of stroke risk factors in patients with lacunae and LVTI. Hypertension was present in 60.4% of patients with lacunae and 50.4% of patients with LVTI without a significant difference \([df=1, P=0.094, OR=1.5\; 95\%CI\; (0.93-2.42)]\). Diabetes and hypercholesterolemia were significantly more frequent in patients with lacunar stroke \([df=1, P<0.001, OR=1.97, 95\%CI\; (1.04-3.73), \text{and} \; df=1, P<0.001, OR=9.8, 95\%CI\; (4.23,9)\), respectively). The frequency of smoking and TIA was not significantly different between patients with lacunae and LVTI \([df=1, P=0.59, OR=0.83, 95\%CI\; (0.42-1.63), \text{and} \; df=1, P=0.37, OR=1.36, 95\%CI\; (0.68-2.72), \text{respectively}]\).

Atrial fibrillation was significantly more frequent in patients with LVTI \([df=1, P=0.034, OR=1.97, 95\%CI\; (1.04-3.73)\) and \(df=1, P<0.001, OR=9.8, 95\%CI\; (4.23,9), \text{respectively}]\). The frequency of ipsilateral and symptomatic \((\geq 50\%)\) carotid or vertebrobasilar territory stenosis was not significantly different in lacunae and LVTI patients \([df=1, P=0.127, OR=0.67, 95\%CI\; (0.39-1.12)]\). Ipsilateral middle cerebral artery stenosis was found by transcranial Doppler in 2 patients with lacunar infarction and 6 patients with LVTI. Table 1 shows the frequency of various etiologic mechanisms in our 96 lacunar and 252 LVTI patients.

Atherosclerosis was the most common etiology in our lacunar stroke patients, followed by uncertain etiologies and cardioembolism. Both atherosclerosis and cardioembolism were found in 15.2% of our lacunar stroke patients. Comparison of each etiology between lacunar and LVTI patients revealed insignificant differences.

### Discussion

The role of hypertension in the pathogenesis of lacune has been overemphasized. Hypertension was almost universal in the early reports of lacunar patients.\(^{11}\) Hypertension is present in 60.4% of our lacunar stroke patients and in 68% of lacunar patients in New York population.\(^{12}\) In our study group, the frequency of hypertension was not significantly different in lacunar and LVTI patients. Our results suggest that hypertension is no more important in the pathogenesis of lacunar infarction than stroke due to atherosclerosis of major cerebral arteries. This raises the possibility of mechanisms other than small-vessel disease in non-hypertensive patients. The apparent excess of hypertension in lacunar infarction was confined to studies in which the presence of hypertension favored a diagnosis of lacunar infarction.\(^{13}\) The increased prevalence of hypertension among those with lacunar infarction, in studies defining ischemic stroke subtypes by a risk factor-free classification, was marginal.\(^{13}\) Diabetes mellitus was present in 40.4% of our lacunar stroke patients, a rate similar to that reported by Horowitz et al.\(^{12}\) There was a significant excess of diabetes in lacunar versus non-lacunar infarction in studies using a classification in which diabetes favors a diagnosis of lacunar infarction.\(^{13}\) Diabetes and hypercholesterolemia in our stroke patients were significantly more frequent than in LVTI patients. Baumgartner et al. found that raised cholesterol predisposes more to lacunar than non-lacunar infarction.\(^{14}\) Frequency of smoking and TIA was not significantly different in our two study groups. A similar study of stroke risk factors was conducted in the Netherlands.\(^{15}\) The frequency of all of the atherosclerotic risk factors including hypertension, diabetes, hypercholesterolemia, smoking and TIA was not significantly different in lacunar and LVTI patients in the Netherlands study.\(^{15}\) Carotid stenosis ipsilateral to the symptomatic lacune was found in 27.1% of our lacunar stroke patients. An ipsilateral potential carotid source of embolism was identified in 23% of Horowitz et al.\(^{12}\) and 28% of Ghika et al.\(^{16}\) lacunar patients. In lacunar stroke patients, carotid stenosis on the ipsilateral side is more common than on the contralateral side.\(^{13}\) Carotid endarterectomy appears to reduce the subsequent risk of lacunar, as well as LVTI stroke in patients with carotid disease.\(^{13}\) A potential cardiac source of embolism was found in 12.5% of our patients, 18% of Horowitz patients\(^ {12}\) and 17% of Ghika patients\(^ {16}\) with lacunar stroke.
Atrial fibrillation was much more frequent in our patients with LVTI stroke. However, the frequency of cardioembolism alone or in combination with atherosclerosis was not significantly different in our lacunar and LVTI patients. The reason is that unlike western countries, non-valvular atrial fibrillation is not the most common cause of cardioembolic stroke in our patients.  

Rheumatic valvular disease is the most common cause of cardioembolic strokes in the Iranian population. Based on transthoracic echocardiography, 5-20% of patients with lacunae have a potential cardiac source of embolism. Lacunae occurring during cardiac catheterization with an embolic mechanism have been reported. An overview of previous studies indicates that one-third of lacunar stroke patients have a potential large-artery or cardiac source of embolism. In fourteen studies about lacunae, there was a stronger association between atrial fibrillation and non-lacunar stroke than lacunar infarction. The association was more pronounced in studies in which atrial fibrillation and ipsilateral carotid stenosis favored a diagnosis of non-lacunar infarction and was less extreme among studies with risk factor-free subtype definitions. Hypertension is not significantly more common in patients who develop lacunae than in those with cortical infarctions. Our results reduce the generality of the hypothesis that hypertension and diabetes are particularly associated with lacunar infarction. Cardioembolism and artery-to-artery embolism are important but less common mechanisms of lacunae.

References