

Risk Factors for Leukoaraiosis in North American and Iranian Stroke Patients

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Abstract

Background: Leukoaraiosis (LA) or white matter thinning and rarefaction are common in stroke patients. This pilot double-center study was designed to evaluate LA risk factors in stroke patients.

Methods: This cross sectional study was conducted on 100 consecutive stroke patients in Walter Mackenzie Hospital, Canada and 100 consecutive stroke patients in Valie-Asr Hospital, Iran in 2004. Diagnosis of ischemic stroke and LA was performed by stroke neurologists using CT scan. The effects of race, gender, age groups, hypertension, diabetes, hypercholesterolemia and smoking on frequency rate of LA were evaluated.

Results: The frequency rate of LA was the same in stroke patients living in North America or Iran. But, the frequency of LA in female stroke patients was more frequent than males ($p < 0.005$). LA was significantly predominant in stroke patients with age ≥ 65 -yrs than those with age < 65 -yrs ($p < 0.05$). The frequency of LA was significant in hypertensive patients. However, the frequency rate of LA was not influenced by diabetes, hypercholesterolemia and smoking.

Conclusion: Female gender, age and hypertension seem to be the main risk factors of leukoaraiosis. In addition, there was no difference between the frequency rates of LA in patients living in Iran or North America.

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Keywords • Leukoaraiosis • stroke • risk factors • gender

Introduction

Leukoaraiosis (LA) means thinning or rarefaction of cerebral white matter which is often located at periventricular and subcortical areas.¹ LA is a common neuroradiologic finding in elderly people. LA is classified as a variant of atherosclerosis that selectively involves the penetrating arterioles of periventricular areas, resulting in chronic ischemia.¹ LA represents deeply placed watershed infarcts caused by hypoperfusion in the distal deep arterial or arteriolar territories. Combination of atherosclerosis and reduced perfusion pressure results in multiple lacunar infarctions, ischemic demyelination and gliosis.² There is substantial evidence that LA is associated with stroke, independent of other stroke risk factors.³ LA has prognostic implications because its presence increases the risk of stroke not only in

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patients with transient ischemic attacks and minor stroke, but also in general population.³ In other view, history of stroke was found to be the most important predictor of LA.⁴ In neuroimaging, the incidence and severity of LA is related to age and some vascular risk factors. The fact that despite intensive control of vascular risk factors in the last decades, incidence of LA and vascular dementia has not changed significantly,² reveals that further research in this area is needed. Hence, this pilot double-center study was designed for evaluation of LA risk factors.

Patients and Methods

The protocol was approved by Ethical committees of Birjand University of Medical Science, Birjand, Iran and an informed consent was obtained from patients or their guardians. A cross sectional study was carried out on 200 consecutive ischemic stroke patients admitted to Walter Mackenzie Hospital, Canada, and Valie-Asr Hospital, Birjand University of Medical Sciences, Birjand, Iran during 2004. Stroke patients with mild deficits or transient ischemic attack were excluded from the study. Diagnosis of ischemic stroke was made by stroke neurologists based on WHO criteria.⁵ All of our stroke patients in the two centers underwent brain CT scan within 24-48 hours post stroke according to formal procedures.^{3,6} Although, MRI is more sensitive for detection of LA, but its specificity is lower than CT imaging.^{1,6} Furthermore, brain CT scan is a routine neuroimaging of stroke in these two centers.

The study was performed with high resolution Toshiba scan device using standard method and one centimeter brain cuts in both centers.⁷ A stroke neurologist reviewed all of the brain scan films in both hospitals. LA was defined on baseline CT scan as symmetrical hypodensity in periventricular and subcortical white matter.^{7,8} These are poorly marginated patchy or punctuate and non-displacing lucencies.^{6,7} In neuroimaging, cerebral infarctions were classified as small vessel and large vessel territory infarcts. Small vessel territory or lacunar infarcts defined as subcortical infarcts with a diameter

of less than 2 cm and large vessel territory infarcts consisted of cortical infarcts or subcortical infarcts with diameter more than 2 cm.⁶ Patients were divided in to <65 and ≥65 years age groups. Hypertension was defined as using antihypertensive medication or patients with two blood pressure values (at least 1 week apart) of >140/90 mm/Hg.^{2,3} Administration of antidiabetic medication or a fasting blood glucose >6.4 mmol/l were definitions of diabetes mellitus.^{2,3} Hypercholesterolemia assumed as using lipid lowering medication or fasting cholesterol > 5.2 mmol/l or >200 mg/dl.^{2,3} Fasting blood sugar and lipid profile were part of routine investigations performed within the first 48 hrs of stroke. Those who smoked more than five cigarettes per day in recent years, were regarded as smokers.⁹

Statistical analyses

Data on patient's demographics, vascular risk factors and neuroimaging were recorded using questionnaires. The effects of population group, gender, age and vascular risk factors on frequency rate of LA were analyzed using Chi-square, Fishers exact test and multiple logistic regression tests was used and $p < 0.05$ was considered as statistically significant.

Results

Two hundred ischemic stroke patients (98 females, 102 males) with mean age 71.88 ± 10.99 yrs were evaluated. Twenty one percent of North American and Persian stroke patients had LA without difference in population groups (OR=1, CI=0.51-1.98). In age groups < 65-yrs and ≥ 65-yrs, the frequency rate of LA in North American stroke patient was similar with that of Persian stroke patients, (df=1, $p=0.072$), (df=1, $p=0.588$). Stroke female patients with hypertension and with age ≥65 yrs were more prone to LA. However, diabetes, hypercholesterolemia and smoking did not have a distinct influence on the frequency rate of LA. LA was more frequent in patients with small vessel than large vessel territory infarcts. Table 1 represents frequency rate of leukoaraiosis risk factors in 200 stroke patients.

Table 1: Frequency rate of leukoaraiosis risk factors in 200 strokes.

Risk factor	Odds ratio	95% CI	P value
Female/Male ratio	3.295	1.54-7.05	0.002
Age>65-yrs/≤65-yrs	2.54	1.003-6.433	0.049
Hypertension	1.36	0.672-2.75	0.04
Diabetes	0.922	0.416-2.04	0.841
Hypercholesterolemia	0.864	0.401-1.864	0.709
Smoke	0.618	0.201-1.896	0.400
Lacunae	0.603	0.287-1.266	0.181

Discussion

The frequency rate of LA was the same in North American and Persian population groups. A study, on white and black Americans, has showed similar results.¹⁰ However, in a study performed in the United States indicated that white population was more prone for ventricular enlargement and widening of cortical sulci than black ones.¹¹ The risk of developing LA in our female patients was 3.29 times more than of men which is congruent with the Rotterdam scan study, reported by de Leeuw, et al.¹² This may particularly at later age underlie the reasons for seeing higher incidence of dementia in women than in men.¹² Gender preponderance for LA was not found in the US and Turkish studies.^{9,13} However, a similar study conducted in Bethesda, Maryland, showed male gender predominance of LA.¹¹ The frequency of LA in our study groups lies in the range of 4.3% to 38% the same as of other studies around the world.² This wide range of prevalence might be due to differences in neuroimaging technology and LA definitions.

This clinical study was conducted by using CT scan technology. Although MRI has more sensitivity than CT scan (100% vs. 72%) for detection of LA, however its specificity is lower than CT scan (88% vs. 100%).^{1,6} Furthermore, brain CT scan is the routine neuroimaging of stroke and performance of expensive MRI only for research has ethical limitation. The pilot studies performed in these two centers was conducted in patients with ischemic stroke and could not show any differences between the frequency rate of LA in North American and Persian general population.

In our study groups, by adjusting gender effect the risk of developing LA in stroke patients aged ≥ 65 -yrs was 2.54 times more than in patients < 65 yrs. Hachinski et al. have reported the presence of LA in 11% of stroke patients in their fourth decade of their life and 65% of in those in the seventh decade of their life.^{1,2} In fact aging and hypertension are important risk factors of LA in our stroke patients. LA was strongly associated with age and hypertension in other case-control and cohort studies.^{10,11,13-15} Only about one fourth of elderly patients with hypertension develop LA. This suggests that except age and vascular risk factors, genetic factors may participate in the development of LA.³

Although, some studies has indicated that other vascular risk factors such as diabetes, hypercholesterolemia and smoking may highly affect the development of LA,¹⁵⁻¹⁸ the results of our study and others did not support this con-

clusion.^{6,19} Wiszniewska et al. had confirmed that LA is significantly more frequent in patients with small artery disease and lacunar infarction.²⁰ Although LA was more frequent in our stroke patients with lacunar infarction, however this difference was not significant. The reason for this discrepancy could be different indications for admission of patients in two centers. Based on the hypothesis that extensive LA is an indicator of diffuse arteriosclerosis, it is highly plausible that LA has a predictive value for stroke in patients with lacunar infarction. This association could be due to small vessel pathology as stated by Inzitari too.⁴

Conclusion

The results of this study confirm that development of leukoaraiosis is commonly associated with small artery disease and seems to be correlated with hypertension and aging.

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