Leukoaraiosis as a predictor for mortality and morbidity after an acute ischaemic stroke

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ABSTRACT

Introduction: Leukoaraiosis (LA) is a term that defines an abnormal appearance of the subcortical white matter of the brain on neuroimaging. This study was done to evaluate the predictive value of LA in terms of mortality, disability and cognitive decline at three months post-stroke and also to identify the risk factors that are independently associated with LA in a stroke population.

Methods: This was a prospective observational study of all patients with acute ischaemic stroke who were admitted to Hospital Universiti Kebangsaan Malaysia from June to November 2004. A single observer using the pre-defined diagnostic criteria recorded the information on demography, Barthel Index and mini-mental state examination. LA was diagnosed on brain computed tomography alone.

Results: 60 patients were recruited into the study. Three patients (five percent) died and LA was present in 29 patients (48 percent). There was no significant association between LA and mortality (p-value equals 0.89). The independent risk factors that were associated with LA were age (odds-ratio [OR] 4.43; 95 percent confidence interval [CI] 1.28-15.27) and hypertension (OR 14.3; 95 percent CI 1.40-147.42). There was a significant association between LA with early dementia (OR 3.53; 95 percent CI 1.19-10.49). However, LA did not significantly predict any functional disability (Barthel Index is less than 60) in the study population (p-value equals 0.45).

Conclusion: Development of LA correlates significantly with ageing and hypertension. The presence of LA can also predict early cognitive dysfunction but is not associated with functional disability at three months post-stroke.

Keywords: brain imaging, computed tomography, hypertension, ischaemic stroke, leukoariosis, stroke risk factors

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INTRODUCTION

The World Health Organisation (WHO) (1978) defines stroke as a clinical syndrome typified by rapidly-developing signs of focal or global disturbance of cerebral functions, lasting more than 24 hours or leading to death, with no apparent causes other than of vascular origin.[1] Leukoaraiosis (LA) is a radiological finding that is caused by cerebral ischaemia. It is defined as bilateral patchy or diffuse areas of hypodensity of the subcortical white matter of the brain on brain computed tomography (CT).[2] Brain CT, although less sensitive than magnetic resonance (MR) imaging, may be more specific in diagnosing LA.[3] The frequency of LA increases with age, but an increased risk of LA has also been connected to hypertension and heart disease.[4] Pathological studies have consistently linked LA with demyelination, gliosis, necrosis, cavitation, and vacuolisation, conditions commonly associated with cerebrovascular disease.[5] Selective injury to the hemispheric white matter has been noted in a limited number of human conditions characterised by hypoxia/ischaemia to the brain.[6]

Although physical function limitations following stroke have a major impact on the quality of life, the currently-used measurement instruments are not able to completely assess the stroke severity. The most common measure of stroke-related physical disability is the Barthel Index (BI). It is considered to be the best of the activities of daily living measurement scales. The internal consistency reliability coefficient was 0.87 in one study.[7,8] The prevalence of dementia within the first year after stroke ranges from 9% to 30% in hospital-based studies, depending on the nature of the sample studied and the definitions used for dementia.[9] Two large studies have recently reported rates of post-stroke cognitive impairment of approximately 40%–55%. Madureira et al found that three months after stroke, 55% of 220 patients

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had evidence of cognitive impairment. Of these, only 6% had dementia.[10] Thus, nearly 50% had mild to moderate cognitive impairment insufficient for a diagnosis of dementia. The present study was done to evaluate the predictive value of LA in terms of mortality, disability and cognitive decline at three months post-stroke and also to identify the risk factors that are independently associated with LA in a stroke population.

METHODS

In a single hospital, Hospital Universiti Kebangsaan Malaysia, a cohort of patients was identified. They included all patients with acute ischaemic stroke admitted from June 2004 to November 2004. A total of 60 patients were recruited during the study period. Stroke was defined according to WHO criteria: rapidly-developed clinical signs of focal disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than vascular origin.[1] Brain CT was performed on all the patients for diagnosis of acute ischaemic stroke and LA. LA was diagnosed in this study by subjective assessment by a neurologist or radiologist based on the presence of bilateral patchy or diffuse areas of hypodensity of the subcortical white matter of the brain on brain CT. Patients who had an intracerebral bleed or previous stroke were excluded.

A standardised data sheet was used to record the demographical variables including age, sex, presence of LA and the neurological diagnosis. The following putative risk factors were considered: age, sex, smoking, hypertension, diabetes mellitus, hyperlipidaemia, and ischaemic heart disease. Patients were followed-up at three months post-stroke in the neuromedical clinic and were examined for functional ability based on the BI, which evaluates ten different activities of daily life and ranges in total score from 0 to100 points. Patients were divided into three groups, namely: BI < 41 (severely disabled), BI 41–60 (moderately disabled), BI > 60 (mildly disabled).[7,8]

The mini-mental state examination (MMSE) was also performed during the follow-up. MMSE is a brief test of cognitive status that measures the following areas: orientation to time and place, immediate and delayed verbal recall memory, attention, concentration, naming, repetition, following a three-step command, following a written command, sentence writing, and visual-motor copying. Scores on the MMSE ranged from 0–30, with scores of 23 or lower considered to have early cognitive dysfunction. Cognitive impairment was defined as the presence of a MMSE score of less than 24.[9] All statistical analyses were performed using the Statistical Package for Social Science version 12.0 (SPSS Inc, Chicago, IL, USA), with statistical significance at 0.05 (two-sided). Univariate analyses were performed on the demographical characteristics and the risk factors, type of stroke and outcome. The relationship between baseline and clinical variables and LA were analysed with the chi-square test. The logistic multiple regression model was used for analysing the risk factors which predicted LA. This study was approved by the institution research and ethics committee of the Faculty of Medicine, Universiti Kebangsaan Malaysia (project code: FF-178-2004).

Table I. Characteristics of patients with acute ischaemic stroke with and without leukoaraiosis.

	Leukoaraiosis	
	No (%) 31 (52.0)	Yes (%) 29 (48.0)
Age (years)	62.31 ± 10.14	64.23 ± 9.47
Male	21 (67.0)	18 (62.0)
Diagnosis		
Lacunar infarct	24 (77.4)	21(93.1)
MCA infarct	2 (6.5)	1 (3.4)
ACA infarct	2 (6.5)	0 (0)
PCA infarct	3 (9.6)	1 (3.4)

MCA: middle cerebral artery; ACA: anterior cerebral artery; PCA: posterior cerebral artery

RESULTS

During the five-month study period, 60 patients with acute ischaemic stroke were identified. The majority of the patients were male (39, 65%). The youngest patient was a 37-year-old Chinese male smoker who had a lacunar infarct with underlying type II diabetes mellitus and hypertension. The oldest patient was an 82-year-old Indian male smoker who had a lacunar infarct with underlying hypertension and hyperlipidaemia. The mean age was 63.17 ± 10.53 years. The ethnic composition of the patients was as follows: 36 Chinese (60%), 19 Malays (32%) and five Indians (8%).

The majority of patients (51, 85%) presented with lacunar infarcts, followed by four patients (7%) with posterior cerebral infarct, three patients (5%) with middle cerebral artery infarct, and two patients (3%) had anterior cerebral artery infarct. Out of the 60 patients studied, LA was present in 29 patients (48%) (Table I). Over the three-month follow-up study period, three patients (5%) died. These patients had died at home and the cause was not known at that time. Out of the three deaths, two patients had LA. Using the chi-square test, LA was not significantly associated with mortality ($p = 0.89$). LA was independently associated with early cognitive dysfunction (MMSE < 24) (odds-ratio [OR] 3.53; 95% confidence interval [CI] 1.19–10.49; $p = 0.03$). However, it was not significantly associated with any functional disability (BI ≤ 60) in the study population ($p = 0.35$) (Table II).

Table II. Association of leukoaraiosis with cognitive dysfunction and functional disability.

	Leukoaraiosis	
	No (%)	Yes (%)
Mini-mental state examination		
≥ 24	23 (74.4)	13 (44.8)
< 24	8 (25.6)	16 (55.2)
Barthel Index		
> 60	28 (90.3)	24 (82.2)
≤ 60	3 (9.7)	5 (17.2)

Table III. Multivariate analysis of parameters analysed for the risk of leukoaraiosis in stroke patients (n = 60).

Parameters studied	Odds-ratio	95% confidence interval	p-value
Hypertension	14.39	1.40–147.2	0.02
Diabetes mellitus	0.85	0.24–2.91	0.85
Hyperlipidaemia	0.14	0.02–1.02	0.053
Ischaemic heart disease	1.92	0.15–23.56	0.61
Alcohol	2.66	0.39–17.91	0.31
Smoking	0.65	0.18–2.36	0.52
Age	4.43	1.28–15.27	0.01

The mean duration of hypertension in patients with LA was 10.85 ± 8.72 years. This was not significant in comparison with the patients without LA (p = 0.41). Using the multiple logistic regression model, the independent risk factors associated with LA were hypertension (OR 14.39; 95% CI 1.40–147.42) and age above 65 years (OR 4.43; 95 % CI 1.28–15.27) (Table III). However, there was no significant relationship between LA and the other risk factors for atherosclerosis-like ischaemic heart disease (p = 0.94), diabetes mellitus (p = 0.99), smoking (p = 0.59), alcohol (p = 0.38), or hyperlipidaemia (p = 0.26) in the univariate analysis.

DISCUSSION

This study was hospital based. Patients were identified using an internationally-recognised definition of stroke. Hypertension was the commonest risk factor present in this study population, followed by hyperlipidaemia, diabetes mellitus, smoking and alcohol. The present study demonstrated LA to be an important predictor for early cognitive dysfunction. It also further strengthens the association between old age and hypertension with LA. The prevalence of LA in this study group was 48%. The prevalence of LA among our patients was higher than that reported by other authors. Hijdra et al reported that 38% of patients hospitalised with cerebrovascular disease had LA on CT.[11] One possible cause for the higher prevalence of LA in this study is that Asian patients are more prone to intracranial stenosis as compared to the Caucasians.[12] Therefore, the Asian population may tend to have a higher incidence of LA/small vessel disease.

The overall mortality rate in this study was 5%. This was lower than other studies. A previous study done in this hospital in 2001 quoted a mortality rate of 11.7%,[13] while the Ege Stroke Registry reported a 30-day mortality of 19.7%.[14] The three patients who died in this study group had all died at home and the nature of their deaths was not exactly known. In this study, there was no significant association found between LA and mortality. The stroke patients with LA were significantly older. Age above 65 years significantly predicted LA. Epidemiological studies have demonstrated a high prevalence of LA in community subjects older than 65 years evaluated by MR imaging.[2] Karsidag et al also proved that ageing was a significant risk factor in the development of LA.[15]

The duration of hypertension that was associated with occurrence of LA was not significant in our study. However, Karsidag et al proved that the duration of hypertension was longer in stroke patients with LA than in stroke patients without LA.[15] Our study also found that hyperlipidaemia was not independently associated with the development of LA. Cholesterol has a controversial role in deep white matter lesions. Although total cholesterol and high density lipoprotein cholesterol concentrations were not significantly associated with the presence of white matter lesions, higher concentrations of total cholesterol tended to be associated with white matter lesions for the younger patients (65–74 years old) in one study.[16]

Alcohol, diabetes mellitus and ischaemic heart disease were not significantly associated with LA in this study. Jorgensen et al showed that moderate daily alcohol intake seemed to be associated with a decreased risk in stroke patients. Even though there were negative findings for ischaemic heart disease, diabetes mellitus and alcohol in a stroke population, it is still possible to have a relationship between LA and these stroke risk factors in individuals without stroke.[17] This study also proved that LA can predict early dementia three months post-stroke by causing early cognitive dysfunction based on the MMSE. Most published studies have assessed cognitive function in ischaemic stroke patients at three months or more after the stroke, with the expectation that cognitive deficits have stabilised at this stage, after a period of initial recovery.[10] The major limitation of using the MMSE in assessing early cognitive dysfunction in this study is that it may not have been accurate enough to recognise early cognitive dysfunction in our study population as the majority of the patients were illiterate. Some of the patients had severe functional disability during the stroke episode, like hemiplegia or expressive dysphasia, and these factors limited the use of the MMSE. Furthermore, the baseline

MMSE was not recorded during the initial period of acute ischaemic stroke, therefore pre-stroke dementia could have been missed. A more sensitive cognitive function test would have been a better screening method to detect early dementia. An association between the extent of LA and post-stroke dementia has been reported.[10] Miyao et al demonstrated that after the first lacunar infarction, the prevalence of dementia is higher in patients with LA.[18]

In this study, we failed to prove any significant association between LA and functional disability as determined by the BI post-stroke. However, performance in basic activities of daily living, as measured by the BI, is strongly associated with stroke severity. There are several studies showing that small vessel disease with motor impairment significantly predicts physical dependence.[19] Many recent studies have reported that in elderly individuals, LA is associated with gait dysfunction and reduced mobility.[20] LA appears to be an important prognostic factor in stroke patients. Although the risk of early death after stroke was not increased in patients with LA, it was found to increase the risk of death or dependency three months after an ischaemic stroke. It was also noted to increase the risk of death in patients with lacunar stroke, and to adversely influence the cardiovascular prognosis in patients with a history of stroke with a higher incidence of cardiac failure, repolarisation disturbances, and atrial fibrillation.[21]

The present study demonstrated that the development of LA correlated significantly with ageing and hypertension. The presence of LA can also predict early cognitive dysfunction at three months post-stroke. The presence of LA did not predict functional disability or mortality at three months post-stroke. The association between LA and hypertension warrants vigorous management of high blood pressure in hypertensive patients. Future studies should grade the LA to determine the severity of LA in association with the risk factors studied. We need further research into factors that may be protective against such lesions, so that effective preventive strategies can be put into place.

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