ORIGINAL ARTICLE

The Predictors of Subclinical Cerebral Infarcts in Ischaemic Stroke Patients

B B Hamidon, MMed, J P Joseph, MMed, A A Raymond, FRCP

Department of Medicine, Faculty of Medicine, Hospital Universiti Kebangsaan Malaysia, Jalan Yaacob Latiff, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur

SUMMARY

Subclinical cerebral infarcts (SCI) have been increasingly shown to cause a significant clinical impact. However, there are limited data available on Asian patients. The objectives of this study were to determine the prevalence of SCI in ischaemic stroke patients seen in the Hospital Universiti Kebangsaan Malaysia (HUKM) and to identify its associated risk factors. We evaluated the brain computed tomography (CT) evidence of subclinical infarcts in ischaemic stroke patients. The patients were selected from those who were on regular follow up in the neurology clinic following an ischaemic stroke. The risk factors associated with subclinical infarct were documented. The brain CTs were done during acute admission and reviewed for SCI. Sixty-one patients were enrolled in this study. Twenty-two (36.1%) out of the 61 patients had SCI. The risk factors for SCI in our study were hypertension (OR 14.16 CI 2.04-97.89), diabetes mellitus (OR 12.48; CI 1.95-79.77) and leukoaraiosis (OR 28.39; CI 2.33-284.16). Subclinical cerebral infarcts were present in about one third of our ischaemic stroke patients. This finding is higher than in previous studies done on Caucasians. Hypertension, diabetes mellitus and leukoaraiosis independently predict SCI.

INTRODUCTION

Subclinical cerebral infarcts (SCI) are lesions that share neuroimaging and neuropathologic characteristics with cerebral infarcts but without any recognized acute stroke clinical symptoms. It is defined as a brain parenchymal lesion of vascular origin, without a history of corresponding symptoms or signs of prior stroke (including transient ischaemic attacks and vascular dementia)[1]. SCI have commonly been detected not only in patients presenting with their first stroke, but also in healthy elderly individuals[2,3]. In the Trial of ORG 10172 in Acute Stroke Treatment or TOAST study, 22.7% had subclinical infarcts on baseline brain CT[4]. A study by Shinkawa et al. revealed that about 13% of the subjects in a consecutive autopsy series had cerebral infarcts without clinical stroke during their lives[5]. Fisher pointed out the frequently silent nature of infarcts in a clinicopathological study in which 77% of patients lacked a history of stroke or evidence of neurological deficit, despite the presence of lacunar infarcts at autopsy[6].

Although SCI in the past was considered to be of minimal significance, it is now becoming more and more important in clinical practice. This is due to the increasing evidence of SCI being associated with future stroke, cognitive impairment and to a lesser extent, functional disability[7,8]. Several studies have shown that Asians have more intracranial atherosclerotic disease compared to Caucasians[9]. This difference may also translate into a different composition of SCI in these two groups. Currently there is limited data on SCI in Asians. Therefore, this study was conducted to provide some evidence on SCI in stroke patients in Malaysia.

MATERIALS AND METHODS

Consecutive ischaemic stroke patients attending the neurology clinic of HUKM over a 3-month period were recruited. Once selection was made, written informed consent was obtained from the patient. The patients selected would have presented earlier with an ischaemic stroke to the HUKM general medical wards. A detailed history was taken and examination performed to ascertain that the symptomatic stroke only occurred once, during the admission. The brain CTs were assessed for evidence of subclinical infarcts, not associated with the symptomatic site. Leukoaraiosis was also analysed from the brain CTs. In terms of patient characteristics, patients were divided into two groups (with and without SCI) and compared. The data were presented as mean for the age (normally distributed) and numbers for the other parameters. To test for difference in proportions between the two groups, the chi square test was used. The difference in mean was tested using the independent Student's t-test. SCI was determined as the dependent variable. A multiple logistic regression model was used for the dependent variable. The independent variables included demographic variables; age, hypertension, diabetes mellitus, smoking, hyperlipidaemia and leukoaraiosis. These risk factors for SCI were entered as categorical data. All probability values shown were based on the Wald test. Odds ratios (OR) with 95% confidence intervals (CI) were used to estimate the effects of each factor. The event per variable ratio was intended to be more than ten. All statistical analyses were performed with the SPSS 12.0 package, with statistical significance at 0.05 (2-sided).

RESULTS

We recruited 61 ischaemic stroke patients who had attended the neurology clinic for their regular follow up. Twenty-two (36.1%) patients were found to have SCI in their brain CTs.

This article was accepted: 20 March 2007

Corresponding Author: Hamidon Bin Basri, Jabatan Perubatan Fakulti Perubatan UKM, Jalan Yaacob Latiff, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur

Seven patients had more than 1 SCI. Altogether, there were 33 SCI detected. The commonest site of SCI was the basal ganglia area (15, 45.4%), followed by corona radiata (9, 27.3%), occipital region (7, 21.2%) and brainstem (2, 6.1%). The patient characteristics are shown in Table I. Among the patients' characteristics, there were significantly higher incidence of hypertension (86.4% vs 53.8%), diabetes mellitus (72.7% vs 43.6%), smokers (50.0% vs 17.9%), and leucoaraiosis (54.5% vs 5.1%) in the SCI group (Table I). The chosen variables were first subjected to univariate analysis before undergoing multivariate analysis (logistic regression). There were no interactions between the variables tested. The risk factors for SCI in our study were hypertension (OR 14.16 CI 2.04-97.89), diabetes mellitus (OR 12.48; CI 1.95-79.77) and leukoaraiosis (OR 28.39; CI 2.33-284.16). The results of the multiple logistic regression is presented in Table II.

DISCUSSION

The prevalence of SCI in our population was 36.1%. This result is higher than in other reports using brain CT to assess SCI in pre-existing stroke patients[4]. This could be due to the fact that the incidence of intracranial atherosclerosis is higher in Asians[7]. However, this should be taken with caution, as the study is not intended to compare between Asians and Caucasians. Furthermore, the number of patients studied was small and included all three Asian races (Malays, Chinese and Indians). The evidence for intracranial disease was mainly for Asian Chinese. The improvement in the resolution of CT scanners could be another possible explanation for the higher rate of silent infarct in our study. Furthermore, the other previous studies also used different methodologies and measured different endpoints.

The commonest site of SCI was the basal ganglia region. This is consistent with previous studies[4,7]. In our population, the independent risk factors for SCI were hypertension, diabetes mellitus and leukoaraiosis. Hypertension and diabetes have been shown previously to be risk factors for SCI. These risk factors are responsible for the progression of atherosclerotic and lypohyalinotic changes in small arteries of the brain and result in dysregulation of cerebral flow and metabolism[3], leading to small silent cerebral infarcts. Older age has been associated with SCI in several studies[7,10]. In our study, there was a significant difference between the mean age; the SCI group being older by about nine years. However, on logistic regression analysis, age was not an independent predictor of SCI. This may be due to the small number of patients recruited. With more events (SCI), the possibility of age being a significant predictor is higher in the logistic regression model. Leukoaraiosis is a non-specific term that refers to white-matter rarefaction, which is seen as hypodense lesions on brain CT[11]. It was reported to occur in 9% to 19% of the elderly and in 3% to 44% of stroke patients[12]. It is also an important prognostic factor in stroke patients and has been strongly associated with stroke recurrence[13]. Leukoaraiosis was significantly associated with SCI in our study. To the best of our knowledge, there are no well-established studies on leukoaraiosis as a risk for SCI.

The main limitation of this study was the small number of patients recruited. However, this was enough to show a significant difference in the parameters studied to assess the risk factors for SCI. This is mainly because of the high percentage of SCI found in our study. The other limitation was the use of CT for detecting SCI. From previous studies, MRI undoubtedly has been shown to be a more sensitive tool to assess SCI[10,14]. Nonetheless, MRI is an expensive screening method and is not done on all patients with stroke. Therefore, a cheaper and more practical alternative is CT. Brain CT is compulsory and must be done in all stroke cases. Since the clinical importance of SCI is now becoming more and more apparent, a detailed and meticulous report on SCI should be undertaken in all acute stroke brain scans for future prognostication. As discussed earlier, the possible impact of SCI on patients are the development of future strokes, cognitive impairment and, functional disability. Whether treatment with antiplatelet agents in patients with SCI will

Table I: Patient characteristics

		Silent cerebral infarct (SCI)		
		Yes (n=22)	No (n=39)	p value
Age (SD)		67.8 (11.93)	58.7 (11.89)	0.035
Sex	Male	15 (68.2%)	29 (74.4%)	0.41
	Female	7 (31.8%)	10 (25.6%)	0.59
Race	Malay	11 (50%)	14 (35.9%)	0.60
	Chinese	8 (36.4%)	23 (59.0%)	0.11
	Indian	3 (13.6%)	2 (5.1%)	0.34
Clinical Features	Hypertension	19 (86.4%)	21 (53.8%)	0.012
	Diabetes Mellitus	16 (72.7%)	17 (43.6%)	0.035
	Hyper-Lipidaemia	17 (77.3%)	28 (71.8%)	0.76
	Smoker	11 (50.0%)	7 (17.9%)	0.02
Leucoaraiosis		12 (54.5%)	2 (5.1%)	0.0001

Table II: Multivariate analysis on predictors of SCI

	OR	95% CI	p value
Age	16.44	1.42 -190.11	0.250
Hypertension	14.16	2.04 - 97.89	0.007
Diabetes Mellitus	12.48	1.95 - 79.77	0.008
Smoking	5.55	0.943- 32.61	0.058
Leukoaraiosis	28.39	2.33 -284.16	0.002
Hyperlipidaemia	1.62	0.238-110	0.621

prevent these outcomes is another question that has to be answered by future studies.

In conclusion, our study has shown that SCI was found in a significantly high proportion of our patients. The independent predictors of developing SCI were diabetes mellitus, hypertension and leukoaraiosis. Since SCI is an important predictor of dementia and future stroke, the next step of future research would probably be in the form of screening for SCI in high-risk patients and its cost-effectiveness.

REFERENCES

1. Masuda J, Nabika T, Notsu Y. Silent stroke: pathogenesis, genetic factors and clinical implications as a risk factor. Curr Opin Neurol 2001; 14: 77-82.
2. Kobayashi S, Okada K, Yamashita K. Incidence of silent lacunar lesion in normal adults and its relation to cerebral blood flow and risk factors. Stroke 1991; 22: 1379-83.
3. Price TR, Manolio TA, Kromal RA, Kittner SJ, Yue NC. Silent brain infarction on magnetic resonance imaging and neurological abnormalities in community-dwelling older adults. The Cardiovascular Health Study (CHS) Collaborative Research Group.Stroke 1997; 28: 1158-64.
4. Davis PH, Clarke WR, Bendixen BH *et al*. The TOAST investigators Silent cerebral infarction in patients enrolled in the TOAST study. Neurology 1996; 46: 942-48.
5. Shinkawa A, Ueda K, Kiyohara Y, *et al*. Silent Cerebral Infarction in a Community-Based Autopsy Series in Japan. Stroke 1995; 26: 380-85.
6. Fisher CM. Lacunes, small, deep cerebral infarcts. Neurology 1965; 15: 774-84.
7. Bernick C, Kuller L, Dulberg C *et al*. Silent MRI infarcts and the risk of future stroke; the cardiovascular health study. Neurology 2001; 57: 1222-29.
8. Kuller LH, Lopez OL, Jagust WJ *et al*. Determinants of vascular dementia in Cardiovascular Health Cognition Study. Neurology 2005; 10: 1548-52.
9. Wong KS. Intracranial stenosis in Chinese patients with acute stroke. Neurology 1998; 50: 812-13.
10. Vermeer SE, Hollander M, Van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM. Silent infarcts and white matter lesions increase stroke risk in the general population: Rotterdam Scan study. Stroke 2003; 34: 1126-29.
11. Starkstein SE, Almeida OP. Understanding cognitive impairment and dementia: stroke studies. Curr Opin Psy 2003; 16: 615-20.
12. Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Leukoaraiosis in Stroke Patients: The Copenhagen Stroke Study. Stroke 1995; 26: 588-92.
13. Henon H, Durieu I, Pasquier,F, Leys D. Leukoaraiosis more than dementia is a predictor of stroke recurrence. Stroke 2003; 34: 2935-40.
14. Neuman HT. New magnetic resonance imaging methods for cerebrovascular disease: emerging clinical applications. Ann Neurol 2000; 47: 559-70.