PAPER

Risk factor profile of cerebral small vessel disease and its subtypes

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J Neurol Neurosurg Psychiatry 2007;**78**:702–706. doi: 10.1136/jnnp.2006.103549

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Received 1 August 2006
Revised 29 November 2006
Accepted 13 December 2006
Published Online First 8 January 2007

Background: The mechanisms of cerebral small vessel disease (SVD) are unclear. Both atherosclerosis and a non-atherosclerotic diffuse arteriopathy have been reported pathologically. Two pathological and radiological subtypes have been suggested: localised atherosclerotic disease in larger perforating arteries causing larger lacunar infarcts without leukoaraiosis, and diffuse disease in smaller arterioles causing multiple smaller lacunar infarcts with leukoaraiosis. If atherosclerosis were important in SVD as a whole or in one particular subtype, one would expect the risk factor profile to be similar to that of cerebral large vessel disease (LVD).

Methods: Risk factor profiles were compared in Caucasian stroke patients with SVD (n = 414), LVD (n = 471) and 734 stroke-free Caucasian population controls. Patients with SVD were subdivided according to the presence or absence of confluent leukoaraiosis, into isolated lacunar infarction (ILI) and ischaemic leukoaraiosis (ILA).

Results: Hypertension was commoner in SVD than LVD (odds ratio (OR) 3.43 (2.32 to 5.07); $p<0.001$) whereas hypercholesterolaemia (OR 0.34 (0.24 to 0.48); $p<0.001$), smoking (OR 0.63 (0.44 to 0.91); $p = 0.012$), myocardial infarction (OR 0.35 (0.20 to 0.59); $p<0.001$) and peripheral vascular disease (OR 0.32 (0.20 to 0.50); $p<0.001$) were commoner in LVD. Among SVD patients, age (OR 1.11 (1.09 to 1.14); $p<0.001$) and hypertension (OR 3.32 (1.56 to 7.07); $p = 0.002$) were associated with ILA and hypercholesterolaemia (OR 0.45 (0.28 to 0.74); $p = 0.002$), diabetes (OR 0.42 (0.21 to 0.84); $p = 0.014$) and myocardial infarction (OR 0.18 (0.06 to 0.52); $p = 0.001$) with ILI.

Conclusion: SVD has a different risk factor profile from the typical atherosclerotic profile found in LVD, with hypertension being important. There are differences in the risk factor profile between the SVD subtypes; the association of ILI with hypercholesterolaemia, diabetes and myocardial infarction may be consistent with a more atherosclerotic aetiology.

The pathogenesis of cerebral small vessel disease (SVD) is incompletely understood. Hypertension is a major risk factor but fails to account for all of the risk.[1] Neuropathological data, particularly soon after a lacunar stroke, are limited because of low case fatality. Pathological vascular abnormalities reported include both a diffuse arteriopathy of the perforating arteries with hyaline deposition, an appearance referred to as lipohyalinosis, and microatheroma.[2]

Based on pathological studies, it has been suggested that there may be two types of SVD that can be differentiated on brain imaging.[3] The first involves atheroma at the origins or proximal portions of the larger (200–800 μm diameter) perforating arteries. This is associated with single or a few larger lacunar infarcts without leukoaraiosis. The second involves a diffuse arteriopathy of the smaller perforating arteries, 40–200 μm in diameter, resulting in multiple smaller lacunar infarcts with leukoaraiosis. Endothelial dysfunction may play an important role in the pathogenesis of this SVD subtype. A reduction in white matter cerebral blood flow[4] and autoregulation,[5] both dependent on nitric oxide released from the endothelium, has been reported in lacunar infarction with leukoaraiosis. Furthermore, circulating markers of endothelial activation are elevated in lacunar infarction with leukoaraiosis,[6] and specific associations have been reported with homocysteine, which is toxic to the endothelium.[7]

One way of obtaining information on pathogenesis is to compare the risk factor profile between different stroke subtypes. If atherosclerosis plays an important role in SVD, one would expect the risk factor profile to be similar to that seen in patients with large artery atherosclerotic stroke. Furthermore, as suggested by pathological studies in SVD, if atherosclerosis is more important in lacunar infarction without leukoaraiosis compared with lacunar infarction with leukoaraiosis, one might expect differences in the risk factor profile between the two proposed subtypes of lacunar stroke, with a more atherosclerotic profile seen in lacunar infarction without leukoaraiosis.

A meta-analysis of four community based clinical studies demonstrated that there are differences in the risk factor profile between ischaemic stroke subtypes.[8] Large vessel disease (LVD) stroke was associated with male sex, smoking and raised cholesterol, while SVD was associated with hypertension. However, there were several limitations to these studies, including small SVD and LVD sample sizes, lack of MRI imaging in all studies, variability in risk factor definition between studies, inclusion of hypertension and diabetes in the SVD definition by some studies which may result in biased risk factor–stroke subtype associations, and failure to prospectively subtype patients using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria in one large stroke cohort used in the meta-analysis. In this same cohort, a significant proportion of patients did not have carotid imaging. It has been shown that subtyping based on clinical presentation alone without imaging of the large arteries cannot reliably distinguish SVD from LVD.[9] Studies have also suggested there may be

Abbreviations: ILA, ischaemic leukoaraiosis; ILI, isolated lacunar infarction; LVD, large vessel disease; MI, myocardial infarction; PVD, peripheral vascular disease; SVD, small vessel disease; TOAST, Trial of Org 10172 in Acute Stroke Treatment

differences in the risk factor profile between the two subtypes of cerebral SVD but data are limited and most studies have been small,[3 10–14] and this was not covered in the meta-analysis above.

In this study, we used a large well-phenotyped group of patients with SVD and LVD to determine differences in the risk factor profile between the two groups. All patients had brain imaging and imaging of the extracranial cerebral arteries. In addition, differences in the risk factor profile between the two proposed subtypes of SVD were determined.

METHODS

Study population

A total of 414 Caucasian patients with SVD were recruited from participating stroke services between 2000 and 2006. From the principal investigator's centre, consecutive patients with lacunar stroke who met the inclusion criteria were prospectively recruited. This included patients with both isolated lacunar stroke and ischaemic leukoaraiosis (ILA). These were recruited as they presented, and clinical details and blood were taken at this time. To increase the numbers of ILA subjects, we also prospectively recruited consecutive patients presenting with ILA to four other specialised stroke centres using the same definition for SVD. Over the same time period, 471 consecutive Caucasian patients with LVD were prospectively recruited from the principal centre. The patient participation rate was 87%. The TOAST criteria[15] were used to subtype ischaemic stroke based on a pathophysiological classification, but were modified such that the presence or absence of risk factors such as hypertension and diabetes was not used in subtyping, to avoid biased risk factor associations.

SVD was defined as a clinical lacunar syndrome[16] with a compatible lesion on MRI or CT. Exclusion criteria included the presence of subcortical infarction >15 mm in diameter or cortical infarction of any size, carotid or vertebral artery stenosis >50% and potential cardiac sources of embolism, defined as high or moderate risk on the TOAST criteria.[15] Patients with evidence of previous subcortical infarction >15 mm in diameter or cortical infarction on imaging were also excluded. LVD stroke was defined as carotid or vertebral artery stenosis >50%. Again, potential cardiac sources of embolism were excluded. From 2000 to 2006, 734 Caucasian community controls free of clinical cerebrovascular disease were also recruited by random sampling from family practices from the same regions of recruitment of SVD and LVD patients. The participation rate in controls was 31%.

All patients and controls completed a standardised study questionnaire and underwent standardised clinical assessment. All patients had brain imaging, imaging of the extracranial cerebral vessels and ECG. Where clinical suspicion was higher for a cardioembolic source, echocardiography was performed (20% of the LVD cohort and 37% of the SVD cohort). Brain imaging was not performed in controls.

The same risk factor definitions were used for patients and controls. Hypertension was defined as persistent elevation of systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg at least 1 week from stroke onset, or current treatment with antihypertensive drugs.[17] Diabetes mellitus was defined as a previous diagnosis of type I or type II diabetes, or at least two random glucose readings of >11.1 mmol/l or fasting blood glucose readings of >7.0 mmol/l.[18] Hypercholesterolaemia was defined as a serum total cholesterol >5.2 mmol/l or current treatment with a statin. A positive smoking history was recorded in those who had smoked at any time in their lives. A previous history of myocardial infarction (MI) and peripheral vascular disease (PVD) was recorded based on clinical history, documented investigations and, for MI, the ECG. The study protocol was approved by the local research ethics committees, and informed consent was obtained from all participants.

Subtyping of SVD

MRI scans were available in 297 patients (72%) with SVD. The remaining 117 patients had CT alone (28%). Leukoaraiosis was graded on MRI or CT using the semiquantitative Fazekas scale which has been shown to reflect pathological severity of SVD in a post-mortem validation study.[19] On the basis of the leukoaraiosis grade, patients were subtyped into two groups: isolated lacunar infarction (ILI: lacunar infarction with absent or mild leukoaraiosis, equivalent to Fazekas grade ⩽2) or ILA (lacunar infarction in the presence of moderate or severe confluent leukoaraiosis, equivalent to Fazekas grade 3) according to a previously validated method.[6] Twenty MRI scans were randomly selected for regrading on a second occasion by the same rater and there was perfect agreement in assignment of subtype (kappa = 1). Patients with SVD on CT were included in the study to avoid selection bias. Eleven patients were identified who had undergone CT within 3 months of their MRI scan. CT scans were assessed blind to clinical details, subtype allocation and MRI appearances. All patients were allocated to the same subtype (ILI or ILA) by either CT or MRI assessment.

Statistical analysis

Univariate and multivariate logistic regression analysis was used to calculate odds ratios, 95% CI and p values. Age, male sex, hypertension, diabetes, hypercholesterolaemia, MI, PVD and smoking were controlled for in the multivariate analysis. PVD was not included in comparisons with normal controls because it was not recorded in all control subjects.

Table 1 Demographics of cerebral small vessel disease, large vessel disease and normal control groups, and univariate comparisons between groups

	Controls (n = 734)	LVD (n = 471)	SVD (n = 414)	LVD vs controls		SVD vs controls		SVD vs LVD	
				OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Age (y)	65.4 (8.7)	67.5 (10.5)	68.8 (10.9)	1.02 (1.01 to 1.04)	<0.001	1.04 (1.03 to 1.05)	<0.001	1.01 (1.00 to 1.02)	0.082
Male sex	485 (66.1)	316 (67.1)	256 (61.8)	0.96 (0.75 to 1.22)	0.716	1.20 (0.94 to 1.54)	0.149	1.26 (0.96 to 1.66)	0.103
Hypertension	428 (58.5)	334 (71.2)	367 (88.6)	1.75 (1.37 to 2.25)	<0.001	5.53 (3.95 to 7.75)	<0.001	3.16 (2.19 to 4.54)	<0.001
Diabetes	37 (5.1)	83 (17.6)	54 (13.0)	4.00 (2.66 to 6.00)	<0.001	2.80 (1.81 to 4.34)	<0.001	0.70 (0.48 to 1.02)	0.061
Hypercholesterolaemia	248 (62.3)	386 (82.5)	259 (62.6)	2.85 (2.08 to 3.89)	<0.001	1.01 (0.76 to 1.34)	0.942	0.36 (0.26 to 0.48)	<0.001
Smoking	432 (58.9)	393 (83.4)	295 (71.4)	3.51 (2.64 to 4.66)	<0.001	1.74 (1.34 to 2.26)	<0.001	0.50 (0.36 to 0.69)	<0.001
MI	46 (6.3)	85 (18.0)	22 (5.3)	3.27 (2.24 to 478)	<0.001	0.83 (0.49 to 1.41)	0.494	0.26 (0.16 to 0.42)	<0.001
PVD	–	108 (23.0)	30 (7.3)	–	–	–	–	0.26 (0.17 to 0.40)	<0.001

LVD, large vessel disease; MI, myocardial infarction; PVD, peripheral vascular disease; SVD, small vessel disease.
Results are given as mean (SD) for continuously distributed data or numbers (%) for categorical data.
OR, 95% CI and p values are for between group univariate comparisons.

Table 2 Comparisons between risk factor profiles of cerebral small vessel disease, large vessel disease and normal control groups on multivariate analysis

	LVD vs controls		SVD vs controls		SVD vs LVD	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Age (y)	1.04 (1.02 to 1.05)	<0.001	1.03 (1.02 to 1.05)	<0.001	1.00 (0.99 to 1.02)	0.649
Male sex	1.14 (0.87 to 1.49)	0.354	1.25 (0.95 to 1.65)	0.113	1.33 (0.97 to 1.81)	0.076
Hypertension	1.46 (1.06 to 2.01)	0.020	4.88 (3.34 to 7.15)	<0.001	3.43 (2.32 to 5.07)	<0.001
Diabetes	4.84 (2.71 to 8.66)	<0.001	2.74 (1.51 to 4.97)	0.001	0.77 (0.51 to 1.17)	0.215
Hypercholesterolaemia	2.76 (1.94 to 3.92)	<0.001	0.86 (0.62 to 1.19)	0.363	0.34 (0.24 to 0.48)	<0.001
Smoking	3.64 (2.54 to 5.22)	<0.001	1.84 (1.32 to 2.57)	<0.001	0.63 (0.44 to 0.91)	0.012
MI	2.89 (1.70 to 4.91)	<0.001	0.72 (0.36 to 1.44)	0.354	0.35 (0.20 to 0.59)	<0.001
PVD	–	–	–		0.32 (0.20 to 0.50)	<0.001

LVD, large vessel disease; MI, myocardial infarction; PVD, peripheral vascular disease; SVD, small vessel disease.
Multivariate analysis was performed using all risk factor variables in the table, with the exception of PVD, for comparisons involving the normal control group. OR, 95% CI and p values are shown.

RESULTS

Subject characteristics

Demographics and risk factor profiles for patients with SVD and LVD and for controls are shown in table 1.

Differences between patients and controls

Risk factor subtype associations before and after controlling for age, sex and vascular risk factors are shown in tables 1 and 2. The following were risk factors for SVD compared with controls on both univariate (table 1) and multivariate (table 2) analyses: age, hypertension, diabetes and smoking. In LVD patients, age, hypertension, diabetes, hypercholesterolaemia, MI and smoking were more common compared with controls on univariate analysis (table 1). After multivariate analysis, these associations persisted (table 2).

Differences between SVD and LVD

On comparison between SVD and LVD, univariate analysis demonstrated significant associations between SVD and hypertension, and between LVD and hypercholesterolaemia, MI, PVD and smoking (table 1). These associations persisted after multivariate analysis (table 2).

Differences between subtypes of SVD

Table 3 shows the clinical characteristics of the SVD subgroups. A total of 185 patients with SVD (44.7%) were classified as ILI and 229 patients (55.3%) as ILA. On univariate analysis, patients with ILA were significantly older than patients with ILI, and hypertension was significantly increased in patients with ILA compared with ILI. By contrast, hypercholesterolaemia, diabetes and MI were significantly increased in patients with ILI compared with ILA. The significant associations between ILA and age, ILA and hypertension, and between ILI and hypercholesterolaemia, diabetes and MI persisted after multivariate analysis (table 3).

Statin use in patients with SVD and LVD, and in SVD subtypes

Patients with hypercholesterolaemic SVD were less likely to be treated with a statin (29.0%) compared with hypercholesterolaemic LVD patients (46.6%) (table 4). This difference was significant after adjusting for age, sex and vascular risk factors. In the LVD cohort, hypercholesterolaemic patients were more likely to be on a statin if they were hypertensive ($p = 0.001$), diabetic ($p = 0.002$) and had a previous MI ($p = 0.003$), and in the SVD cohort, hypercholesterolaemic patients were more likely to be on a statin if they had previous MI ($p = 0.019$) after controlling for age, sex and vascular risk factors. Within SVD, hypercholesterolaemic patients with ILA were more likely to be statin treated compared with patients with ILI after multivariate analysis (table 4).

DISCUSSION

Our results, in a well-phenotyped group of consecutively and prospectively recruited patients, showed clear differences in the risk factor profile between SVD and LVD. In addition, the two subtypes of SVD demonstrated differences in risk factor profile.

LVD was associated with a classical proatherogenic risk factor profile and demonstrated strong associations with age, diabetes, hypercholesterolaemia, smoking and MI. The association between hypertension and LVD, although significant, was weaker. SVD was associated with age, hypertension, diabetes and smoking compared with controls. Comparison between the risk factor profiles of LVD and SVD demonstrated clear

Table 3 Demographics of proposed small vessel disease subtypes: lacunar stroke without ischaemic leukoaraiosis compared with lacunar stroke with moderate to severe leukoaraiosis

			Univariate		Multivariate	
	ILI (n = 185)	ILA (n = 229)	OR (95% CI)	p Value	OR (95% CI)	p Value
Age (y)	63.7 (10.8)	72.8 (9.1)	1.10 (1.07 to 1.12)	<0.001	1.11 (1.09 to 1.14)	<0.001
Male sex	116 (62.7)	140 (61.1)	1.07 (0.72 to 1.59)	0.744	0.93 (0.57 to 1.50)	0.927
Hypertension	153 (82.7)	214 (93.4)	2.98 (1.56 to 5.70)	0.001	3.32 (1.56 to 7.07)	0.002
Diabetes	33 (17.8)	21 (9.2)	0.47 (0.26 to 0.84)	0.010	0.42 (0.21 to 0.84)	0.014
Hypercholesterolaemia	130 (70.3)	129 (56.3)	0.55 (0.36 to 0.82)	0.004	0.45 (0.28 to 0.74)	0.002
Smoking	133 (72.3)	162 (70.7)	0.93 (0.60 to 1.43)	0.731	1.18 (0.71 to 1.97)	0.518
MI	15 (8.1)	7 (3.1)	0.36 (0.14 to 0.90)	0.028	0.18 (0.06 to 0.52)	0.001
PVD	14 (7.6)	16 (7.0)	0.92 (0.44 to 1.94)	0.830	1.15 (0.47 to 2.83)	0.763

ILA, ischaemic leukoaraiosis; ILI, isolated lacunar infarction; MI, myocardial infarction; PVD, peripheral vascular disease.
Results are given as mean (SD) for continuously distributed data or numbers (%) for categorical data.
OR, 95% CI and p values are for between group univariate and multivariate comparisons.

Table 4 Comparison of statin use between patients with large vessel and small vessel disease and between proposed small vessel disease subtypes

	LVD (n = 471)	SVD (n = 414)	ILI (n = 185)	ILA (n = 229)	SVD vs LVD OR* (95% CI)	p Value	ILA vs ILI OR* (95% CI)	p Value
Hypercholesterolaemia	386 (82.5)	259 (62.6)	130 (70.3)	129 (56.3)	0.34 (0.24 to 0.48)	<0.001	0.45 (0.28 to 0.74)	0.002
Proportion of hypercholesterolaemics on statins	180 (46.6)	75 (29.0)	31 (23.8)	44 (34.1)	0.50 (0.35 to 0.73)	<0.001	3.25 (1.63 to 6.47)	0.001

ILA, ischaemic leukoaraiosis; ILI, isolated lacunar infarction; LVD, large vessel disease; SVD, small vessel disease.
*Controlling for age, sex and vascular risk factors.

differences. LVD was strongly associated with hypercholesterolaemia, MI and PVD and, to a lesser degree, smoking. Reflecting this, statin use was increased in hypercholesterolaemic LVD patients compared with SVD patients at the time of stroke. In contrast, SVD was associated with hypertension.

These differences in risk factor profile are consistent with the findings of a meta-analysis of four community based populations.[8] An overall association between SVD and hypertension (OR 1.4 (1.1 to 1.8); p = 0.010) was demonstrated, largely due to the effect of one study when compared with other ischaemic stroke subtypes.[20] The meta-analysis also demonstrated associations between LVD and cholesterol levels and smoking, consistent with our findings. These findings are also consistent with a systematic review, which again identified hypertension as a significant risk factor for lacunar stroke compared with non-lacunar ischaemic stroke.[21] The authors suggested that the current trend of using the TOAST classification system could overestimate the role of hypertension and diabetes in lacunar stroke, as the criteria stipulate that a history of hypertension and diabetes may be useful indicators to the existence of SVD. In our study, we used a modified TOAST classification which did not use risk factors in subtyping. Thus this potential bias does not confound our results.

Boiten *et al* first proposed the hypothesis that two types of SVD may exist.[3] This was based on the neuropathological findings on lacunar stroke from Fisher.[2] It was proposed that single larger lacunar infarcts without leukoaraiosis may be due to atherosclerosis while multiple smaller lacunar infarcts were associated with leukoaraiosis and hypertension, and here a more diffuse arteriopathy may be important. We found that age and hypertension were risk factors for ILA while hypercholesterolaemia, diabetes and MI were risk factors for ILI. The association between age and hypertension and ILA is consistent with data from population studies showing that both are important risk factors for asymptomatic white matter hyperintensity and leukoaraiosis.[22 23] The association of ILI with hypercholesterolaemia and MI may reflect an underlying proatherosclerotic state in the pathogenesis of this SVD subtype. An interesting finding was the reduced statin use in patients with ILI compared with ILA at the time of stroke, suggesting that untreated hypercholesterolaemia in these patients may result in an increased proatherosclerotic environment contributing to ILI pathogenesis which may be prevented by statin use. This preliminary finding would need to be confirmed in large prospective clinical trials. Diabetes mellitus is characterised by both microvascular and macrovascular pathology. Consistent with this, in our study, diabetes was associated with both SVD and LVD compared with normal controls. In the context of SVD, diabetes may result in atheroma at the level of larger perforating arteries.

Table 5 Studies on risk factor associations with small vessel disease subdivisions

	SVD subdivisions	Imaging modality	Risk factors assessed	Multiple lacunar infarcts associate with:
Boiten 1993[3]	SLI (n = 79) MLI (n = 21)	CT	Age, sex, hypertension (>160/90), diabetes (fasting glucose >6 mmol/l), IHD	Leukoaraiosis*
Mast 1995[10]	NLI (n = 453) SLI (n = 144) MLI (n = 40)	CT	Age, sex, hypertension (>160/90), SBP and DBP (mm Hg), diabetes, cardiac disease	Hypertension, diabetes, DBP, inverse cardiac disease
Spolveri 1998[11]	NLI (n = 62) SLI (n = 39) MLI (n = 35)	CT	Age, sex, hypertension (>160/90), DBP and SBP (mm Hg), cardiomegaly (cardiothoracic index >0.5), diabetes (fasting venous plasma glucose >140 mg/dl), serum glucose (mg/dl), smoking, IHD, total cholesterol (mg/dl)	Leukoaraiosis, cardiomegaly, DBP
	SLI (n = 229) MLI (n = 104)			Age, hypertension, leukoaraiosis
De Jong 2002[12]	MLI+leukoaraiosis (n = 63) SLI (no leukoaraiosis) (n = 196)	CT	Age, sex, hypertension (>160/90 mm Hg), diabetes (fasting serum glucose >7 mmol/l), IHD, carotid stenosis	Age, hypertension associated with MLI + leukoaraiosis
Arauz 2003[13]	SLI (n = 39) MLI (n = 136)	MRI	Age, sex, smoking, history of TIA, cardiac disease, hypertension (SBP ≥140 mm Hg), diabetes (WHO criteria), hyperlipidaemia (cholesterol >2.4 g/l, triglyceride levels >1.4 g/l), alcohol intake	Leukoaraiosis, diabetes, haematocrit
Pavlovic 2006[14]	SLI (n = 47) MLI (n = 136)	MRI	Age, sex, history of TIA, hypertension (SBP >140 mm Hg or DBP >90 mm Hg), hypotension (SBP <90 mm Hg or MBP <65 mm Hg) diabetes (fasting serum glucose >7 mmol/l, postprandial glucose >11 mmol/l), cardiac disease, migraine, smoking, haematocrit, fibrinogen, cholesterol (mmol/l), homocysteine (mmol/l), family history of CVD	Age, hypertension, hypotension, SBP, DBP, homocysteine

CVD, cardiovascular disease; DBP, diastolic blood pressure; IHD, ischaemic heart disease; MBP, mean blood pressure; MLI, multiple lacunar infarcts; NLI, non-lacunar infarction; SBP, systolic blood pressure; SLI, single lacunar infarction; TIA, transient ischaemic attack; WHO, World Health Organisation.
*Association with hypertension dependent on presence of ischaemic leukoaraiosis.

These findings support an increasing body of evidence suggesting potential subdivisions within SVD. In patients with ILA, compared with ILI, markers of endothelial dysfunction (intercellular adhesion molecule 1, tissue factor pathway inhibitor and thrombomodulin) were elevated, independent of conventional risk factors.[6] Furthermore, elevated homocysteine was demonstrated in ILA compared with ILI.[7] The association with homocysteine was no longer significant after controlling for the circulating endothelial markers, suggesting homocysteine was mediating its effect through endothelial dysfunction. Further support for differences between the two subtypes of SVD is provided by candidate gene association studies which have shown differential associations with genes involved in homocysteine metabolism and endothelial function.[7 24]

Some smaller studies compared risk factor profiles between SVD subtypes. These are summarised in table 5. Only two, in small populations, with small numbers of single lacunar infarctions, used MRI for subtyping.[13 14] Only three studies looked for associations with raised cholesterol.[11 13 14] The most common associations were between age, hypertension and diabetes, with both multiple lacunar infarction and lacunar stroke with leukoaraiosis. Interpretation is complicated because some studies divided patients into those with single lacunar infarcts and those with multiple lacunar infarcts regardless of the presence of leukoaraiosis. With the widespread use of MRI allowing the detection of smaller asymptomatic lacunar infarcts, and more sensitive identification of leukoaraiosis, increasingly studies are separating patients on the basis of lacunar infarction with or without confluent leukoaraiosis.

The strengths of our study included the consecutive, prospective recruitment of a well-phenotyped group of patients. All subjects had brain imaging, the majority MRI, and all had imaging of the extracranial cerebral arteries. Clinical classification systems, such as the Oxfordshire Community Stroke Project system, have been widely used to subtype stroke. Their use can lead to misclassification in many patients. A study demonstrated that up to 39% of patients presenting clinically with a lacunar syndrome had a non-lacunar infarct on CT.[9] This potential inaccuracy could weaken associations between risk factors and specific stroke subtypes. A further strength was that we used a classification system which was not dependent on risk factor profiles which may have introduced bias.

In this study, although the same risk factor assessment was used for cases and controls, the normal controls did not have MRI. This was both for logistic reasons and also because in our experience this markedly reduces recruitment rates and therefore can introduce bias; for example, those agreeing to have MRI and those not agreeing may differ. None of our controls had symptomatic SVD as this was an exclusion criterion. Not excluding controls with asymptomatic SVD detected on MRI would, if anything, reduce associations between risk factors and disease. However, any effect is likely to be limited. In a recent community based MRI study in 116 healthy individuals, aged 50–89 years, free of symptomatic cardiovascular disease from the same region as this study, asymptomatic lacunar infarcts were present in only 5 (4.3%) and leukoaraiosis (>grade 2, as defined in this study) in 14 (11.9%).[25]

In summary, our results show that the risk factor profile for SVD as a whole differs from the typical proatherogenic profile seen in patients with large artery stroke. This suggests that the pathophysiological process is likely to differ and therefore different treatment approaches may be required. Consistent with previous studies, our findings emphasise the importance of hypertension as a risk factor for SVD as a whole but especially in confluent leukoaraiosis. Our results provide some support for the hypothesis that there are different types of SVD, with hypercholesterolaemia and MI in particular reflecting an underlying atherosclerotic state in patients with lacunar infarction in the absence of confluent leukoaraiosis.

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Usman Khan is supported by a Stroke Association grant (Prog 3)

Competing interests: None.

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