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Are risk factors of cerebral small vessel disease differ from those in patients with high atherothrombotic risk without cerebrovascular disease?

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ABSTRACT

Knowledge of risk factors for cerebral small vessel disease (CSVD) may generate hypothesis regarding possible targets for prevention. Our aim was to evaluate if atherothrombotic risk factors differ between patients with CSVD and with subjects without cerebrovascular disease but with high cardiovascular (CVD) risk. A single-center, cohort study was performed in consecutive patients with different CSVD manifestations. The study group consisted of 205 patients: 52 with lacunar stroke (LS), 20 with subcortical hemorrhagic stroke (HS), 50 with vascular dementia (VaD), 28 with vascular parkinsonism (VaP) and 55 controls (CG) with high CVD risk (35 with atherosclerotic CVD, 20 with 10-year risk of CVD with SCORE≥5). Logistic regression was used to analyze the influence of clinical and laboratory data on the occurrence of CSVD. Mean age, sex distribution, prevalence of smoking, hyperlipidemia, peripheral artery disease and obesity were similar in CSVD and CG. The factors significantly associated with CSVD compared to controls were diabetes mellitus, polymetabolic syndrome, elevated systolic blood pressure, low levels of eGFR, HDL, albumin and high uric acid, fibrinogen, fasting glucose, HbA1c and intima medic thickness ($p < 0.05$). Hypertension, chronic kidney disease and elevated fasting blood glucose were related to LS and HS ($p < 0.1$). Diabetes was significantly associated with LS and VaD while smoking and low total cholesterol were related to HS ($p < 0.1$). The study confirms that risk factors profile for CSVD differs from subjects with proatherogenic profile without history of cerebrovascular disease. Our results also support that unique risk factors profiles exist for different manifestations of the CSVD..

Keywords: cerebral small vessel disease, risk factors, lacunar stroke, vascular dementia, vascular parkinsonism.

Introduction

Cerebral small vessel disease (CSVD) is one of the most important and common microangiopathy [1]. It can cause several different types of distinct or overlapping clinical presentations: recurrent lacunar strokes (LS), deep haemorrhagic strokes (HS), vascular dementia (VaD) and vascular parkinsonism (VaP). The main MRI imaging features are inter-related and include lacunes, intracerebral hemorrhages and white matter

lesions (WMLs) which are frequently found even in asymptomatic elderly people. Although CSVD is considered to result from cerebral arteriolar occlusive disease, classical cardiovascular risk factors are not consistently common in patients with CSVD and latest studies provided evidence, that they can explain only minority of the variance in radiological features [2]. These findings are challenging the traditional view that classical risk factors play a role in CSVD genesis and indicate that pathophysiology of CSVD may be independent from that of atherosclerotic large artery disease [3]. It is also speculated that the exact mechanisms of distinct clinical CSVD manifestations differ and they may be attributable to either burden, lack of control of traditional vascular risk factors and also are influenced by other hemodynamic or inflammatory factors [4]. Due to lack of effective casual treatment, the control and identification of CSVD-specific modifiable risk factors is of increased importance for secondary prevention of ischemic brain lesions [5]. Although asymptomatic radiological CSVD markers e.g. WMLs or lacunes are frequently found in patients with coronary or peripheral artery disease, the comparisons of risk factor profiles between patients with different manifestations of CSVD and patients with high vascular risk but without cerebrovascular disease have not been reported so far. If atherosclerosis were important in CSVD as a whole or in one particular subtype, one would expect the risk factor profile to be similar or even aggravated to that of large vessel disease. Considering the wide spectrum of radiological and clinical picture of CSVD, we hypothesized that associated atherothrombotic risk factors differ between patients with CSVD and subjects without cerebrovascular disease but with high vascular risk.

In this single-center, prospective, cohort study, we compared prevalence of traditional risk factor profiles between patients with different CSVD manifestations and controls with high atherothrombotic risk free of clinical and radiological markers of CSVD.

Material and Methods

Participants

The present investigation is nested in the of SHEF-CSVD Study (Significance of HEmodynamic and hemostatic Factors in the course of different manifestations of Cerebral Small Vessel Disease) [6]. The studied group consisted of 150 consecutive patients: with first-ever recent LS (n = 52) or deep HS (n = 20), VaP (n = 28) and VaD (n = 50) and 55 controls (CG) recruited between December 2011 and June 2014 from patients treated in the Outpatient Department. The study protocol and methods have been thoroughly described elsewhere [5].

In brief, the SVD group consisted of consecutive patients with a first ever recent LS or HS or newly diagnosed VaD and VaP presumed to be caused by CSVD with evidence of typical findings on neuroimaging (MRI). All patients were independent (total Barthel Index ≥ 80 points) and did not have severe dementia (MMSE ≥ 12 points) [7]. The patients were diagnosed according to typical radiological and clinical picture: LS - according to the OCSP Criteria; VaD and VaP after exclusion of other neurodegenerative conditions with the use of clinical tools easily applied in clinical practice: Hurtig criteria or NINDS-AIREN criteria with Modified Hachinski Ischemic Scale ≥7 points, respectively [8, 9, 10]. Patients with recurrent LS or strategic single-infarct dementia or with post-stroke VaD or VaP were excluded. The mean time from first symptoms of cognitive impairment or appearance of parkinsonian symptoms to enrollment was 23.2 ± 10 months in VaD and 25 ± 10 months in VaP (p = 0.5). The control group consisted of patients without history of cerebrovascular disease and with high cardiovascular risk assessed according to the European Society of Cardiology and the European Atherosclerosis Society Guidelines (2011) [11]. High risk was recognized in patients with: documented cardiovascular disease (CVD) – coronary artery disease (CAD) or peripheral arterial disease (PAD); diabetes (type 2 or type 1 diabetes with target organ damage e.g. microalbuminuria); moderate to severe chronic kidney disease (CKD; glomerular filtration rate (GFR) ≤ 60 ml/min/1.73 m^2); or markedly elevated single risk factors such as familial dyslipidemias and severe hypertension (systolic blood pressure (SBP) ≥ 180 mm Hg and/or diastolic blood pressure (DBP) ≥ 110 mm Hg); or 10-year risk of total CVD ≥ 5% (estimated using the Systemic Coronary Risk Estimation (SCORE) risk assessment charts according to gender, smoking status, age, blood pressure (BP) and total cholesterol (TC))

[12]. All participants were aged between 60 and 90 years. Patients with significant stenosis (≥ 50%) of a major extracranial or intracranial artery, atrial fibrillation, non-SVD related WMLs, life expectancy of less than 6 months, and MRI contraindications were excluded.

Study procedures

To prevent confounding by hyperacute phase responses, all LS and HS patients underwent study procedures at least 2 weeks (mean 19.4 ± 4.1 days) after their index strokes. We assessed eGFR and serum total cholesterol (TC), HDL, LDL, triglycerides (TG), fasting glucose (FG), HbA1c, homocysteine, fibrinogen (FBG), albumin and uric acid (UA) levels for all participants. All patients had MRI examination before entering the study. We categorized MRI findings according to STRIVE (Standards for Reporting Vascular Changes on Neuroimaging) guidelines as a reference standard [13]. The simple modified Fazekas rating scale was used to estimate the extent of the periventricular and deep WMLs. Grade 2 (n = 83; 55.3%) or 3 (n = 45; 30%) WMLs were present in 80.3% patients with CSVD. There was no significant difference between mean Fazekas score in LS, HS, VaD and VaP (respectively, 2.18 ± 0.6, 2.3 ± 0.65, 2.04 ± 0.78, 2.11 ± 0.68; $p > 0.1$). Controls were included only in case of normal MRI scans (Grade 0). To determine baseline BP control (24h mean systolic (SBP) and diastolic BP (DBP) we performed 24h ABPM using a validated portable non-invasive oscillometric device (Schiller MT-300). Assessments of carotid intima-media thickness (IMT) were performed according to previously validated criteria by colour-flow B-mode Doppler ultrasonography by a same experienced sonographer. The IMT was defined as the distance between the leading edge of the lumen-intima echo and the leading edge of the media-adventitia echo [14].

Based on clinical history, documented investigations and physical examination at baseline, we evaluated major atherothrombotic risk factors. Hypertension was defined as persistent elevation of systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg at least 1 week from stroke onset, or current treatment with antihypertensive drugs. Diabetes mellitus was defined as a previous diagnosis of type I or type II diabetes, or at least two random glucose readings of ≥ 200 mg/dL or FG ≥ 126 mg/dL. Hypercholesterolaemia was defined as a serum TC ≥ 200 mg/dL or current treatment with a statin. The following criteria were used to diagnose polymetabolic syndrome (PS): waist circumference ≥ 102 cm in men or ≥ 88 cm in women; HDL ≤ 40 mg/dL in men and ≤ 50 mg/dL in women or on drug treatment; elevated SBP ≥ 130 mmHg or ≥ 85 mmHg DBP or on drug treatment; elevated TG ≥ 150 mg/dL or on drug treatment; and elevated FG ≥ 100 mg/dL or on treatment for diabetes [15]. Coronary artery disease was defined in patients with stable angina, prior MI, prior percutaneous revascularization, coronary artery bypass graft, angiographically proven coronary atherosclerosis, or reliable non-invasive evidence of myocardial ischemia [16].

Statistical analysis

Quantitative and qualitative demographic characteristics were summarized, and data were tabulated and tested for normality with the Shapiro-Wilk test. Categorical data were presented as frequencies and compared using the Chi-square, factorial logistic regression, or Fisher's exact test, where appropriate. Continuous data were reported as means ± SD and compared using paired t tests, non-normal data were analyzed using non parametric tests. The one way ANOVA and chi-square test were used to assess statistical differences of data between study groups with *post hoc* Tukey's HSD test used for comparisons between CSVD subgroups. Logistic regression was used to calculate odds ratios (ORs) with 95% confidence intervals (CI) to assess the strength of association between clinical and laboratory data with CSVD vs CG (gender and age-adjusted). For continuous variables the ORs per 1-SD increase was used. A probability value of $p < 0.05$ was considered significant. All data are presented as mean ± SD values. All analyses were performed using Statistica 12 software (StatSoft Inc, USA).

This study complied with the Declaration of Helsinki. All participants signed an informed consent form. This study was approved by the local Medical Ethics Committee.

Results

The comparison of risk factors between patients with CSVD and CG is presented in **Table 1**. Mean

age, sex distribution, prevalence of smoking and hyperlipidemia, PAD and obesity were similar in both groups. Patients with CSVD had a higher prevalence of PS, diabetes, hypertension with elevated 24h SBP, CKD, and lower prevalence of CAD compared to CG ($p < 0.05$). All controls had high CVD risk: 35 patients (63%) had documented symptomatic large artery disease (CAD or PAD), 3 (5.5%) had diabetes and CKD, 2 (3.6%) had diabetes alone, and the remaining 15 (27%) patients had elevated 10-year risk of CVD (SCORE ≥ 5%) caused by other cardiovascular risk factors. Patients with CSVD (n = 94, 62.6%) less often than CG (100%) met criteria for high CVD risk, however the difference was not statistically significant ($p = 0.1$). Among all patients with CSVD 30 (26%) had CAD or PAD, 16 (10.6%) had diabetes and CKD, 65 (43%) had diabetes alone, 17 (11.3%) had calculated SCORE ≥ 5%. No patients from either group had severe hypertension or familial dyslipidemia. The frequency of antiplatelet use in CG and LS, VaP or VaD (respectively, 43.6% vs 83%, 50%, 70%, $p = 0.13$) or statin use (57.4% vs 86,5%, 54%, 60%, $p = 0.8$) recorded at baseline was similar. It was however lower in HS comparing to other study groups (respectively, 15% and 10%, $p < 0.05$). Mean levels of fibrinogen, FG and HbA1c, UA, homocysteine, IMT values were higher and HDL and albumin levels were lower in CSVD than in CG.

There was no difference in frequency of bad control of glycaemia (HbA1c ≥ 7.5%) between dia-

Table 1. Comparison of clinical and laboratory data of patients with CSVD and controls

	CG (n = 55)	CSVD (n = 150)	LS (n = 52)	HS (n = 20)	VaP (n = 28)	VaD (n = 50)	p#
Age (y)	72 (5.9)	72.4 (8.4)	69.9 (8.7)	74.1 (10.4)	72.3 (6.24)	74.4 (7.9)**	.04
Female sex n (%)	25 (45.5)	76 (50)	19 (37)	10 (50)	10 (36)	37 (74)**	.01
Hypertension	43 (78.2)	132 (88)*	49 (94)*	19 (95)*	20 (71.4)	44 (88)	.01
24h - MAP (mmHg)	90.64 (9.8)	94.98 (13.05)	95.02 (12.9)	99.77 (19.4)*	91.24 (11.14)	95.24 (11.1)	.46
SBP (mmHg)	125.3 (18)	133.9 (17.2)**	136.5 (18.3)**	137.1 (21.8)*	128.8 (13)	132.9 (15.3)*	.33
DBP (mmHg)	74.8 (8.2)	75.53 (12.5)	74.24 (11.7)	81.1 (19.7)	72.2 (10.3)	77 (10)	.32
CAD	22 (40)	29 (19)*	10 (19)*	3 (15)	3 (11)	13 (26)	.39
Diabetes mellitus	20 (37)	81 (54)*	29 (56)	10 (50)	14 (50)	28 (56)	.9
HbA1c (%)	5.9 (0.6)	6.3 (1)**	6.57 (1.22)**	5.9 (0.4)	6.3 (1) *	6.2 (0.9)*	.1
FG (mg/dL)	103.1 (20)	123.2 (44.9)**	132 (51.47)**	134.2 (44.6)**	113 (32.7)	115 (41.7)*	.12
Current smoking	15 (27.3)	49 (32.7)	18 (34.6)	9 (45)	11 (39.3)	11 (22)	.2
Hyperlipidemia	43 (78)	107 (71.3)	39 (75)	11 (55)*	20 (71.4)	37 (74)	.37
LDL (mg/dL)	114.6 (36.9)	108.6 (36.5)	109.28 (38.8)	112.45 (28.7)	107.4 (34)	109.5 (39.4)	.81
HDL (mg/dL)	56.5 (17.5)	51.3 (16.7)*	45.9 (9.9)**	58.7 (20.3)	54.9 (13.5)	50.8 (21.4)	.01
TG (mg/dL)	126 (142)	126 (76.8)	147.9 (110)	109.5 (46)	126.3 (54.1)	111.8 (46.6)	.06
TC (mg/dL)	192.2 (38.9)	182.9(42.4)	178.6 (42)	185 (34)	187.5 (43.1)	188.5 (45.3)	.51
PAD	13 (23.6)	27 (18)	8 (15)	4 (21)	6 (21.4)	4 (8)	.1
BMI	26.4 (4.3)	27 (5.3)	28.5 (5.99)*	26.4 (5.4)	25.4 (3.6)	26.7 (4.8)	.1
Obesity (BMI > 30)	11 (20)	37 (24.7)	18 (34.6)	2 (10)	5 (18)	12 (24)	.12
PS	13 (23.6)	63 (42)*	25 (48)**	8 (40)	9 (32)	21 (42)	.5
CKD	3 (5.5)	25 (16)*	10 (19)*	5 (25)*	5 (18)*	5 (10)*	.4
eGFR (ml/min)	99.9 (22.3)	77.2 (24.6)**	78.21 (27.87)**	74.3 (19.7)**	70.2 (22.2) **	79.6 (22.4)**	.38
Albumin (g/dL)	4.5 (0.52)	3.7 (0.7)**	3.7 (0.7)*	3.6 (0.6)*	3.9 (0.6)*	3.7 (0.9)*	.5
Fibrinogen (mg/dl)	284.2 (70.2)	352 (86.9)**	349.7 (76.6)*	359.9 (78.9)*	343.4 (99)*	357.7 (95)*	.4
Uric acid (mg/dl)	4.8 (1.2)	5.9 (1.9)**	6.3 (2.4)*	5.8 (1.8)*	5.9 (1.4)*	5.4 (1.6)*	.2
Vit. B12 (pg/ml)	238.5 (90)	232.3 (119)	209.1 (112)	224 (130)*	299.4 (113.5)*	223.9 (117)	.03
Homocysteine (mg/dl)	13.2 (5.1)	15.3 (6.7)*	13.8 (4.6)	16.9 (7.6)*	17.5 (7.5)**	15.1 (7.5)	.1
IMT (mm)	0.9 (0.1)	1 (0.1)**	1.1 (0.2)**	1 (0.1)	1 (0.1)	1.1 (0.2)*	.01
Antiplatelet treatment	24 (43.6)	95 (63)	33 (62)	9 (45)	19 (67.9)	37 (74)	.1
Statin treatment	31 (57.4)	92 (61)	29 (55)	10 (50)	17 (60)	36 (72)	.11

Values are means (±SD) for continuously distributed data or numbers (%) for categorical data
ANOVA and $\chi 2$ difference between CSVD groups; *Significant difference between studied group vs control subjects ($p < 0.05$). ** <0.01
CSVD – cerebral small vessel disease; CG – control group; LS – lacunar stroke; VaD – vascular dementia; VaP – vascular parkinsonism; CAD–coronary artery disease; BMI–body mass index; FG–fasting glucose; PAD – peripheral artery disease; PS–polymetabolic syndrome; CKD – chronic kidney disease; IMT–intima media thickness; MAP–mean arterial pressure; SBP – systolic blood pressure; DBP–diastolic blood pressure

betic patients from CG and CSVD (8.3% vs 20%; p = 0.18), HS (5%, p = 0.3), VaP (21%, p = 0.2) and VaD (13%, p = 0.6) but it was more frequent in patients with LS (31.2%, p = 0.03). In CSVD subjects without diabetes or CKD, mean levels of HbA1c, FG were higher and eGFR was decreased compared to CG (respectively, 5.8 ± 0.31 vs 5.6 ± 0.31%, p < 0.01; 98.4 ± 10.3 vs 93.2 ± 11.8 mg/dL, p = 0.02; 80.4 ± 23.2 vs 99.1 ± 20.7 ml/min, p < 0.01).

The results of ANOVA and chi-square tests showed significant differences between CSVD groups with regard to mean age, IMT, levels of HDL, vit.B12 and distribution of gender, and hypertension. Post hoc analyses showed that hypertension was more prevalent in LS and HS than in VaP (respectively, 94% and 95% vs 71.4%, p < 0.05). Patients with LS had lower HDL (difference between means, -12.5 ± 4.2 mg/dl, p = 0.01) than those with HS and were also younger (-4.5 ± 1.6 years; p = 0.03), were more often males (63% vs 26%, p = 0.01) and had increased IMT comparing with VaD (0.1 ± 0.03 mm, p = 0.02). Mean vit. B12 levels were lower in LS and VaD than in VaP (respectively, -90.2 ± 30.7 and -75.5 ± 30.7 pg/ml, p < 0.05). Males predominated in VaP compared to VaD (64.3% vs 24%, p = 0.01). There was no significant difference in CSVD groups with regard to levels of homocysteine, LDL, TG, TC and control of blood pressure.

Logistic regression analyzes revealed that in contrast to CG, diabetes (OR 2), PS (OR 2.5), eGFR (OR 0.2), HDL (OR 0.5), albumin (OR 0.1), UA (OR 2.4), fibrinogen (OR 2.6), fasting glucose (OR 2.2), HbA1c (OR 2.1), IMT (1.8) and SBP (OR 1.8) were associated with CSVD (**Figure 1**). All CSVD subgroups demonstrated significant association with low eGFR (OR 0.1–0.3), albumin (OR 0.09–0.3) and high levels of fibrinogen (OR 2.1–3.1) or UA (OR 2.3–3.3). Hypertension (OR 4.4–5), SBP (OR 2–2.1), CKD (5.3–6.6) and FG (OR 2.9–3.8) were related to acute CSVD (LS and HS, p < 0.1). Diabetes mellitus was associated with LS (OR 2.2) and VaD (OR 2) while BMI (OR 1.5), PS (OR 3.1) and IMT (OR 3) were exclusively related to LS. Smoking (OR 3.6), low TC (OR 0.6) and prevalence of hyperlipidemia (OR 0.3) were associated solely to HS (p < 0.1). Symptomatic large artery disease: PAD (OR 3.7, 95%CI 1.5–9.2, p < 0.01) and CAD (OR 2.7, 95%CI 1.3–5.4, p < 0.01) were significantly associated with CG.

Discussion

Our study documented that comparing to controls with high CVD risk but free of cerebrovascular disease, PS, diabetes and high SBP were the only clinical factors that significantly influenced the occurrence of CSVD. Moreover, control of modifiable factors appeared to be important as low eGFR, HDL, albumin and high levels of uric acid and fibrinogen significantly increased that risk. Patients with CSVD subgroups shared similar risk factors but there were some differences. Hypertension, SBP, CKD and elevated FG were associated with acute CSVD manifestations (LS and HS), diabetes was related to LS and VaD whilst smoking and low TC were associated with higher risk of HS.

These results are in line with some previous studies. In a systematic review of 16 studies comparing risk factors between patients with different stroke etiology, hypertension and diabetes were more frequent in patients with lacunar than in large vessel strokes [17].There was no association between smoking and hypercholesterolemia with any type of ischemic stroke. In the study of Khan et al patients with LS more frequently had hypertension whereas smoking, hypercholesterolemia, CAD and PAD were more common in non-lacunar stroke [18]. As we recruited patients with marked WMLs (presumably related to lipohyalinosis) and without ultrasound markers of large vessel disease it is not surprising that the most important risk factors in CSVD group were diabetes and metabolic disturbances (such as decreased eGFR) and not hypercholesterolemia and CAD which are strongly related to large vessel disease. Although patients with CSVD more frequently than CG had diabetes and had higher SBP at baseline, the overall atherothrombotic risk was similar in these groups. High incidence of diabetes (54%) may be surprising but several studies showed that diabetes is an independent risk factor for lacunar strokes and WMLs related to CSVD. Lower prevalence of large artery diseases in CSVD group is also unexpected but it was probably related to previously undiagnosed PAD and CAD as systematic evaluation of these diseases is not currently recommended in asymptomatic patients with cerebrovascular disease.

Higher levels of HbA1c and FG were associated with LS but there was no such association with

other CSVD groups. These findings suggest that patients who have abnormally glycosylated end products, as are present in diabetes, may have more lipohyalinosis resulting in decreased perfusion in the territory of penetrating arteries and responsible for LS. This is in line with cross-sectional ARIC study of 1827 community-dwelling participants, which documented that incident lacunes related to lipohyalinosis were associated with diabetes and HbA1c while LDL, hypertension and smoking were associated with lesions presumable caused by microatheroma [19].

Our results demonstrated that low eGFR and albumin, high uric acid and fibrinogen concentrations were independently associated with all clinical manifestations of CSVD. These results are in line with the Northern Manhattan Study and the Rotterdam Scan Study which found that subjects with reduced eGFR had a greater burden of WMLs volumes after controlling for other factors and there is mounting evidence that CKD increases the risk of different cerebrovascular disease including HS [20, 21, 22]. Also previous studies demonstrated strong correlations of serum UA with WMLs and cognitive decline in elderly adults [23, 24]. Several biologically plausible mechanisms activated by UA and CKD could result in development of WMLs through oxidative stress and inflammation, resulting in endothelial dysfunction and vascular damage [25].

Elevated serum fibrinogen in all CSVD subgroups supports the hypothesis that coagulation pathway contributes to the pathogenesis of CSVD. This association was independent of age and type of CSVD manifestations regardless they were acute or chronic. Fibrinogen is a marker of systemic hypercoagulability, inflammation and acts as an important factor in the coagulation cascade. It is also assumed to be a faithful marker of brain-blood-barrier (BBB) dysfunction. Higher serum fibrinogen levels were independently associated with both WMLs and lacunes and in patients with LS and VaD, it was correlated with the extent of leukoaraiosis [1, 2]. Low albumin level in CSVD was also reported in several previous studies which also suggested an inverse association between serum albumin concentrations and stroke risk [3]. The underlying pathophysiology, however, remains unclear. Albumin increases the plasma oncotic pressure, decreases red blood cell sedimentation and viscosity which might favor reperfusion and leads to a better microvascular circulation. It is also recognized as an important antioxidant and a marker of chronic systemic inflammation [4].

There were some important differences in risk factor profile in between CSVD subgroups which support the concept of multiple mechanisms involved in the pathogenesis of these diseases. Diabetes was significantly related only for LS and VaD. This is in line with community-based cross-sectional studies which failed to find an association between diabetes and WMLs and with Helsinki Aging Brain Study in which WMLs were associated with diabetes only in persons <75 years of age [1, 2]. Patients with VaP had higher homocysteine level while higher BMI and hypertension were less prevalent than in LS group. Hiperhomocysteinemia was only marginally related to LS and VaD and that association was stronger in HS. Elevated level of homocysteine can result from a folate deficiency and it can be aggravated in patients with CKD. Positive association with the presence of WMLs is well documented especially in patients with silent strokes or cognitive impairment [3, 4]. Although smoking was a risk factor for HS, we did not find a correlation with LS, VaD, VaP while majority of studies documented that association with WMLs [5]. We also found that hypertension and low prevalence of hyperlipidemia were related to HS. These results are consistent with previous trials which found that hypertension, smoking, alcohol consumption and low cholesterol are linked to subcortical hemorrhage [6, 7]. However, findings on the association between cholesterol levels and CSVD are not consistent. Total cholesterol, LDL and triglycerides were not significantly associated to any CSVD subgroups in our study. Only low HDL was related to VaD and LS and this was in line with the LADIS study which documented that among 639 elderly subjects with some degree of WMLs, incident lacunes were associated with low HDL. Other studies found that lower TC was associated with CSVD and mid-life lower HDL level was associated with late-life WMLs [8, 9, 10]. Also in a population based cohorts, elevated TG and decreasing LDL were associated with severity of all MRI markers of CSVD [11].

There was a similar risk factors profile between VaP and VaD patients although the later had lower HDL and vit. B12 levels. These different risk factor associations with CSVD subtypes may suggest that concomitant neurodegenerative process play an important role both in the VaD and VaP pathogenesis.

We cannot directly compare our results with others because studies on CSVD usually concentrated on LS patients or asymptomatic patients with WMLs. Knowledge of risk factors for CSVD may generate hypothesis regarding possible targets for prevention. The present study adds new data and demonstrates that risk factor profile for CSVD differs from patients with proatherogenic profile without history of cerebrovascular disease and that modifiable risk factors should be targeted for primary or secondary CSVD prevention. Little is known about role of biochemical markers in CSVD pathophysiology and also of the magnitude of effect of classical vascular risk factors in the disease, which makes our data the more important. The advantages of the current study include the relatively well characterized and simultaneously studied patients with different CSVD manifestations, the use of MRI in controls which enabled us to exclude patients with silent radiological markers of CSVD. We also enrolled a well-phenotyped group of patients with rarely studied chronic VaP and VaD. On the other hand our study has some limitations. The major weakness is the potential for random error or selection bias because of the small number of patients and controls included, and the results may not be generalizable to other populations, however this is also a limiting factor in most published reports on the subject. Although patients with VaP and VaD were included to the present study immediately after diagnosis but they were in an advanced stage of their disease therefore it remains unknown whether our results can be applied to less severely affected patients. The study is therefore regarded as hypothesis generating rather than definitive, and a larger study and replication are needed for more robust conclusions.

In summary, our study showed that the risk factor profile for CSVD as a whole differs from subjects with proatherogenic profile without history of cerebrovascular disease. Our results support the concept that CSVD is not homogeneous, and those unique risk factors profiles exist for different clinical manifestations of the disease. Although this observation requires replication to ensure validity, if validated, it lends support to the involvement of multiple or different pathways in the pathogenesis of LS, HS, VaD or VaP. It is important that close association of CSVD with vascular risk factors gives a chance for successful primary and secondary prevention. The identified high-risk patient groups should be subjected to aggressive management of the underlying diseases and closer follow-up.

Figure 1. Impact of risk factors on the occurrence of CSVD adjusted for age and sex (available at request).

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Conflict of interest statement
The authors declare no conflict of interest.

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