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Risk of vascular events in different manifestations of cerebral small vessel disease: A 2-year follow-up study with a control group

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Abstract

Background and purpose: Natural course of cerebral small vessel disease (CSVD) has not yet been thoroughly studied. The aim of the single center study was to establish risk of vascular events or death in different manifestations of CSVD.

Methods: 150 consecutive, functionally independent patients with marked MRI features of CSVD and with recent lacunar stroke (n = 52, LS), deep hemorrhagic stroke (n = 20, HS), vascular parkinsonism (n = 28, VaP), vascular dementia (n = 50, VaD) and 55 controls (CG) with high atherothrombotic risk free of cerebrovascular events were prospectively recruited and followed for 24 months.

Results: Mean age and sex distribution were similar in CSVD and CG but patients with CSVD were less likely to have CAD (19% vs 40%, p = 0.02) and tended to have higher prevalence of diabetes (54% vs 37%, p = 0.11). The risk of vascular events or death was increased in any patients with moderate to severe white matter lesions at baseline MRI (HR 2.0; 95% CI 0.85–7.2), in CSVD (4.56; 95% CI 1.3–14.9) vs CG, regardless of its clinical manifestation: LS or HS (HR 4.70; 95%

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CI 1.3–16.2) and VaD or VaP (HR 4.59; 95% CI 1.3–15.7). Adjustment for confounders did not change the results substantially.

Conclusions: Patients with symptomatic CSVD regardless of the clinical (acute or chronic) manifestation had more than fourfold the risk of vascular events or death in 24 months of observation compared with controls with high atherothrombotic risk free of cerebrovascular events.

Keywords: Cardiology, Internal medicine, Medicine, Neurology

1. Introduction

Cerebral small vessel disease (CSVD) is one of the most important and common vascular diseases of the brain caused by lacunar infarcts, white matter lesions (WMLs), microbleeds (MBs) and intraparenchymal hemorrhage in the cerebral white and deep gray matter (Pantoni, 2010). Although sharing similar risk factors, the pathophysiology of the disease is regarded as independent of that of atherosclerotic large artery disease. CSVD can cause several different types of distinct or overlapping clinical presentations, including recurrent lacunar strokes (LS), deep haemorrhagic strokes (HS), vascular dementia (VaD) and parkinsonism (VaP). CSVD is responsible for 45% of dementias, 30% cases of ischemic and HS and approximately 5% of all cases of parkinsonism. Lacunar ischemic strokes (IS) or HS usually result from acute occlusion or impaired small penetrating arteries mainly due to hypertensive or age-related vasculopathy. Lacunar infarcts can also manifest a silent stroke, which does not have any apparent symptoms. As CSVD gradually develops due to chronic ischemia, it often results into decline of cognition and ultimately leads to VaD or/and impairment of gait, balance and urinary incontinence resulting in VaP. Comparing with Alzheimer's disease, the cognitive impairment due to CSVD is specifically focused on information processing speed and disturbance in frontal-executive functions. In opposite to Parkinson's disease, VaP is characterized by postural instability and falls rather than with upper limb rest tremor or bradykinesia, frequent occurrence of pyramidal signs, early subcortical dementia and a poor or non-sustained response to levodopa. In a patient where the clinical features are suggestive of VaP or VaD the clinical diagnosis is supported by demonstration of diffuse white matter lesions and/or strategic subcortical infarcts in the brain MRI.

The short- and long-term prognosis of CSVD are not well known. In particular, the risk of vascular events in acute and chronic manifestations of CSVD has not been adequately studied so far, and high-risk patients still have to be defined (Norden et al., 2011).

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2. Hypothesis

We hypothesized that long-term prognosis in patients with different clinical pattern of CSVD is worse than in patients with high atherothrombotic risk free of cerebrovascular events.

3. Materials & methods

In this single-center cohort study, we prospectively evaluated risk of any vascular events or death in patients with non-disabling different clinical manifestations of CSVD and in control group (CG) followed for 24 months. The present investigation is embedded in the SHEF-CSVD Study (Significance of HEmodynamic and hemostatic Factors in the course of different manifestations of Cerebral Small Vessel Disease) (Staszewski et al., 2013). The study group consisted of 150 consecutive patients with symptomatic CSVD and 55 controls (CG) without cerebrovascular disease but with high atherothrombotic risk. The patients were recruited from General or Neurological Outpatient Department and prospectively enrolled to the study between December 2011 and June 2014. The study protocol and methods have been thoroughly described elsewhere (Staszewski et al., 2013).

In brief, detailed MRI and neurological examinations, assessments of cognitive function (Mini–Mental State Examination, MMSE), degree of dependence (modified Rankin Scale, mRS) and disability (Barthel index, BI) were performed at baseline. CSVD group consisted of consecutive patients with neuroimaging markers of CSVD, who were physically independent (mRS $\leq$ 3 and BI $\leq$ 80 points) and had no severe dementia (MMSE $\geq$ 12 points) (Schulc et al., 2015). The patients were diagnosed according to typical radiological and clinical picture with the use of simple clinical classification methods: LS – according to the Oxfordshire Community Stroke Project (OCSP) criteria, HS – parenchymal hemorrhage after vascular malformations, coagulopathies, head trauma have been excluded; VaP and VaD – after exclusion of other neurodegenerative conditions and basing on widely accepted criteria and guidelines: Hurtig scale and NINDS-AIREN criteria with Modified Hachinski Ischemic Scale $\geq$7 points, respectively (Bamford et al., 1991; Hurtig, 1993; Chui et al., 1992; Zijlmans et al., 2004). The date of the first-time recording of the VaP and VaD was used to establish the exact start date of these diseases. Basing on the nature of qualifying events, patients were further classified as acute CSVD (LS and HS) or chronic (VaD and VaP). The control group consisted of patients without history of cerebrovascular disease and with high risk of cardiovascular disease (CVD) assessed according to the European Society of Cardiology and the European Atherosclerosis Society Guidelines (Reiner et al., 2011). High risk was recognized in patients with: documented peripheral arterial disease (PAD); coronary artery disease (CAD) – defined as previous myocardial infarction (MI) or acute coronary syndrome, coronary revascularization/bypass

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graft, angiographically proven coronary atherosclerosis or reliable non-invasive evidence of myocardial ischemia (Goblirsch et al., 2013); 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 and total cholesterol (TC)) (Kessler and Joudeth, 2010).

Participants from both groups were aged between 60 and 90 years. All patients had blood pressure measurement performed and recorded at baseline using oscillometric monitor (Omron Healthcare) with a cuff size appropriate for the arm. Atherothrombotic risk factors were evaluated based on medical records, physical examination and comprehensive history available at baseline. Hypertension was defined as persistent elevation of systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥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 mmol/l or fasting blood glucose readings of ≥126 mg/dL. Hypercholesterolaemia was defined as a serum total cholesterol ≥200 mg/dL or current treatment with a statin. All patients received optimal medical treatment, according to guidelines. Patients with post-stroke dementia or strategic single-infarct dementia, significant stenosis (≥50%) of a major extracranial or intracranial artery, atrial fibrillation, non-CSVD related WMLs (e.g. due to migraine, vasculitis, multiple sclerosis, CADASIL, life expectancy of less than 6 months, and MRI contraindications were excluded.

We categorized MRI findings according to STRIVE (Standards for Reporting Vascular Changes on Neuroimaging) guidelines as a reference standard (Wardlaw et al., 2013). All MRI scans were obtained using the same scanner (GE Healthcare 1.5T scanner). We used imaging with standard T2- weighted, FLAIR and gradient echo sequences. Lacunes were defined as small ≤15 mm, subcortical lesions of similar signal to CSF (i.e., increased signal on T2-weighted, decreased signal on FLAIR and T1-weighted images), cerebral MBs were defined as small (<5 mm), homogeneous, round foci of low signal intensity on T2*-weighted images in basal ganglia, thalamus, white matter, or cortico-subcortical junction. Periventricular and deep WMLs were visualized on T2 and PD/FLAIR images as ill-defined hyperintensities ≥5 mm. The simple modified Fazekas rating scale was used to estimate the extent of the per ventricular and deep WMLs (Fazekas et al., 1987). Mild WMLs (grade 1) was defined as punctate lesions in the deep white matter with a maximum diameter of 9 mm for a single lesion and of 20 mm for grouped

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lesions. Moderate WMLs (grade 2) were early confluent lesions of 10–20 mm single lesions and ≥20 mm grouped lesions in any diameter, and no more than connecting bridges between the individual lesions. Severe WMLs (grade 3) were single lesions or confluent areas of hyperintensity of ≥20 mm in any diameter. Imaging features of CSVD were used as radiological markers of the presence and severity of CSVD in the study and they were rated for the presence of lacunes, WMLs, MBs, and enarged perivascular spaces (PVS) according to a recommended visual CSVD scale (Staals et al., 2014). One point on CSVD scale was awarded if (early) confluent deep WMLs (Fazekas score 2 and 3) or irregular periventricular hyperintensities extending into the deep white matter (Fazekas score 3) or when 1 or more lacunes or MBs were present. We defined perivascular spaces (PVS) as small (≤3 mm) punctate (if perpendicular) and linear (if longitudinal to the plane of scan) hyperintensities on T2 images. One point was awarded if moderate to extensive (10–25 or >25) enlarged PVS were present. Finally the presence of each of the above markers produced a minimum score of 0 and a maximum of 4, representing the total MRI load of CSVD. All patients in CSVD group had at least grade 1 WMLs in Fazekas scale, those in CG were included only following normal MRI.

Data regarding vascular events during the study flow and/or cause of death (classified according to the ICD-10) was obtained at 24-month follow-up visit from the patients or both from treating physician, and/or general practitioner or medical records. Patients with incomplete follow-up were censored at the last time observation. The main outcome event was time to any vascular event or death. Vascular events were further classified as cerebrovascular events (hemorrhagic or ischemic stroke or TIA), cardiovascular events (MI or coronary intervention for stable angina or other peripheral vascular intervention). Vascular death was defined as any cardiovascular or cerebrovascular death or sudden death (Hicks et al., 2014). Non-cardiovascular death was defined as any death with a specific cause that is not thought to be CVD in nature. Undetermined cause of death referred to a death not attributable to one of the above categories. Ischemic and hemorrhagic strokes were defined based on typical clinical features associated with a relevant findings on diagnostic brain imaging. Myocardial infarction was defined as a clinical or pathologic event caused by myocardial ischemia in which there was evidence of myocardial injury or necrosis with a rise of cardiac biomarkers, along with supportive evidence in the form of typical symptoms, suggestive electrocardiographic changes, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. Peripheral vascular intervention was defined as a catheter-based or open surgical procedure designed to improve arterial or venous blood flow or otherwise modify or revise vascular conduits.

This study complied with the Declaration of Helsinki. All participants from both groups signed an informed consent form. This study was approved by the local

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Medical Ethics Committee and was supported by the Polish Ministry of Science and Higher Education as a research project of the Military Institute of Medicine (Warsaw, Poland, study number N N402 473840).

3.1. Analysis

Log-normal data were compared using paired t-tests, non-normal data were analyzed using nonparametric tests, the chi-square test was used for comparisons of categorical variables. The difference between baseline risk factors was compared between CSVD patients and CG. Kaplan–Meier method was used to estimate the event-free survival, study groups were compared using Cox regression. Adjusted hazard ratios (HRs) and 95% CIs were calculated with fixed entry of a pre-defined set of potential confounders (age, sex, vascular co-morbidity and risk factors) selected on the basis of clinical plausibility and previous literature reviews and measured at the baseline visit. Dead or dependent at 24-months follow-up was analyzed using Cox logistic regression. We did not control for baseline WMLs because it may distort estimates of change in longitudinal studies. 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).

4. Results

4.1. Patient characteristics

Study comprised of 205 patients: 150 with CSVD: 52 with first ever recent LS, 20 with HS, 28 with VaP and 50 with subcortical VaD and 55 controls. The estimated mean time from disease onset to enrollment was 17 ± 2.1 days in HS; 17.5 ± 3.8 days in LS; 25.5 ± 11 months in VaD and 27.5 ± 14 months in VaP. 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. Mean age, sex distribution, frequency of smoking, hypertension, PAD and smoking were similar in CSVD and CG but patients with CSVD had less often diagnosed CAD, had higher baseline SBP and tended to have higher prevalence of diabetes. 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 (Table 1). 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%,

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Table 1. Baseline characteristics of patients with cerebral small vessel disease (CSVD) and control group (CG).

	CSVD group	CG	*p*
N (%)	150 (73)	55 (27)	
Index event type:		–	–
Lacunar stroke	52 (35)		
Hemorrhagic stroke	20 (13)		
Vascular Parkinsonism	28 (19)		
Vascular Dementia	50 (33)		
Age, mean (±SD) years	72.4 (8.4)	72 (5.9)	0.40
Female sex, No. (%)	76 (50)	25 (45.5)	0.32
Hypertension	132 (88)	43 (78)	0.24
Coronary artery disease	29 (19)	22 (40)	0.02
Diabetes mellitus	81 (54)	20 (37)	0.11
Current smoking	49 (33)	15 (27)	0.26
Hyperlipidemia	107 (71)	43 (78)	0.23
Peripheral arterial disease	27 (18)	13 (23.6)	0.31
CKD (GFR ≤ 60 ml/min/1.73 m2)	16 (10.6)	3 (5.5)	0.19
Total cholesterol [mg/dl]	182.9(42.4)	192.2 (38.9)	0.17
TG [mg/dl]	126 (76.8)	125.8 (142)	0.2
Baseline SBP/DBP [mmHg]	134(17)/76 (12.5)	125(18)/75 (8.2)	0.01/0.8
BMI, mean (±SD, kg/m^2)	27 (5.3)	26.6 (4.3)	0.56
Obesity (BMI > 30 kg/m^2)	36 (24)	11 (20)	0.69
Antiplatelet use	95 (63)	24 (43.6)	0.13
Statin use	92 (61)	31 (57.4)	0.8

BMI – body mass index; CKD – chronic kidney disease; TG – tryglicerides; SBP – systolic blood pressure; DBP – diastolic blood pressure.
Values are means (±SD) or numbers of patients (%).

54%, 60%, p = 0.8) was similar. It was however lower in HS comparing to other study groups (respectively, 15% and 10%, $p < 0.05$).

Baseline total CSVD load on MRI assessed in CSVD scale was significantly higher in CSVD (mean ± SD: 2.13 ± 0.7) than in CG (0.49 ± 0.5; $p < 0.01$) but there was no significant difference between CSVD groups (LS 2.14 ± 0.6; VaP 2.11 ± 0.7; HS 2.3 ± 0.6; VaD 2.02 ± 0.8; p = 0.5). Grade 2 (n = 83; 55.3%) or 3 (n = 45;30%) WMLs were present in majority of patients with CSVD (80.3%).

4.2. All-cause mortality and vascular events

Information on the outcome was available from 97% of the enrolled patients, 4 patients (2 in VaD and 2 in CG) were lost to follow-up. The mean follow-up time

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in the studied population was 22.9 ± 4.2 months (378.75 person-years): 22.4 ± 4.8 months (271.25 person-years) in CSVD and 23.4 ± 3 months (109.2 person-years) in CG (p = 0.02). Eighteen patients (12%) died in CSVD group and none in CG group. The cause of death was vascular related in 9 (50%) patients due to cardiovascular (fatal myocardial infarction, n = 4; and sudden cardiac death, n = 4) and cerebrovascular disease (fatal hemorrhagic stroke, n = 1); nonvascular in 3 (16%) (infection, n = 2; malignant neoplasm, n = 1) and undetermined in 6 (34%) patients. There were 30 nonfatal vascular events in CSVD: 25 cerebrovascular (24 lacunar strokes, 1 intracranial hemorrhage) and 5 cardiovascular events (myocardial infarctions and angioplasty for PAD) and only 3 events in CG (1 lacunar stroke, 2 myocardial infarctions) (Table 2). Mortality rates in patients with acute (LS and HS) and chronic CSVD manifestations (VaD and VaP) were similar (respectively, 11/72 (15.2%) vs 7/78 (9%), p = 0.13). The frequency of main outcome events (respectively, 24/72 (33%) and 24/78 (30.7%), p = 0.72) and cerebrovascular or cardiovascular events (9/72 (12.5%) vs 16/78 (20.5%), p = 0.2 and 4/72 (5.5%) vs 1/78 (1.3%), p = 0.25) in these groups did not differ significantly. Kaplan-Meier survival curves by CSVD group showed significantly higher risk comparing with CG (log rank p = 0.01) (Fig. 1). Patients with CSVD were at a significantly higher risk for main outcome (HR 4.56) or IS (HR 9.73) compared with CG (Table 3). The risk for main outcome did not change significantly after adjustments for antiplatelet (HR 3.9, 95%CI 1.1–15.5) or statin use (HR 4.3, 95% CI 1.2–14.2). The sensitivity analyses for patients with chronic CSVD or Fazekas Grade 2 or 3 WMLs gave similar results. However, there were no significant differences between acute and chronic manifestations of CSVD with regard to risk of main outcome (HR 1.03; 95%CI 0.5–2.0) or IS (HR 0.57; 95% CI 0.2–1.4) but there was a trend toward increased risk of death from any cause in acute CSVD (HR 2.49; 95% CI 0.9–6.6) which was related to higher risk in patients with HS comparing with other CSVD groups (vs VaD; HR 11.1; 95% CI 2.9–41.8; LS HR 10.3; 95% CI 2.1–49.5 and VaP HR 2.97; 95% CI 0.8–10). In comparison to patients with mild WMLs patients with Fazekas Grade 2 or 3 had a trend toward a higher risk of vascular events or death (HR 2.0; 95% CI 0.85–7.2) but not IS (HR 1.8; 95 %CI 0.4–8.7).

5. Discussion

Despite this considerable clinical and societal impact, the causes and course in different clinical manifestations of CSVD are poorly understood. In this prospective, cohort study with 24 months follow-up, we have documented that CSVD increased more than fourfold the risk of future vascular events or death compared to patients with high atherothrombotic risk but without cerebrovascular disease. The risk of death or vascular events did not depend on acute or chronic type of CSVD manifestations. This risk increased when moderate to severe WMLs

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Table 2. The cause and numbers of different outcome events in patients with cerebral small vessel disease (CSVD) and in control group (CG).

Studied group	Angioplasty for PAD	Non-fatal ischemic stroke	Non-fatal myocardial infarction	Non-fatal intracranial hemorrhage	Vascular death	Non vascular or undetermined death	Main outcome
CG, n(%)	0	1 (1.8)	2 (3.6)	0	0	0	3 (5.4)
CSVD	2 (1,3)	24 (16)	3 (2)	1 (0.7)	9 (6)	9 (6)	48 (32)
LS	2 (3,5)	5 (9.6)	2 (3.8)	0	2 (3.8)	0	11 (21)
HS	0	3 (15)	0	1 (5)	3 (15)	6 (30)	13 (65)
VaP	0	2 (7.1)	1 (3.5)	0	1 (3.5)	3 (10.7)	7 (25)
VaD	0	14 (28)	0	0	3 (6)	0	17 (34)

LS – lacunar stroke; HS – hemorrhagic stroke; VaP – vascular parkinsonism; VaD – vascular dementia; PAD – peripheral arterial disease.

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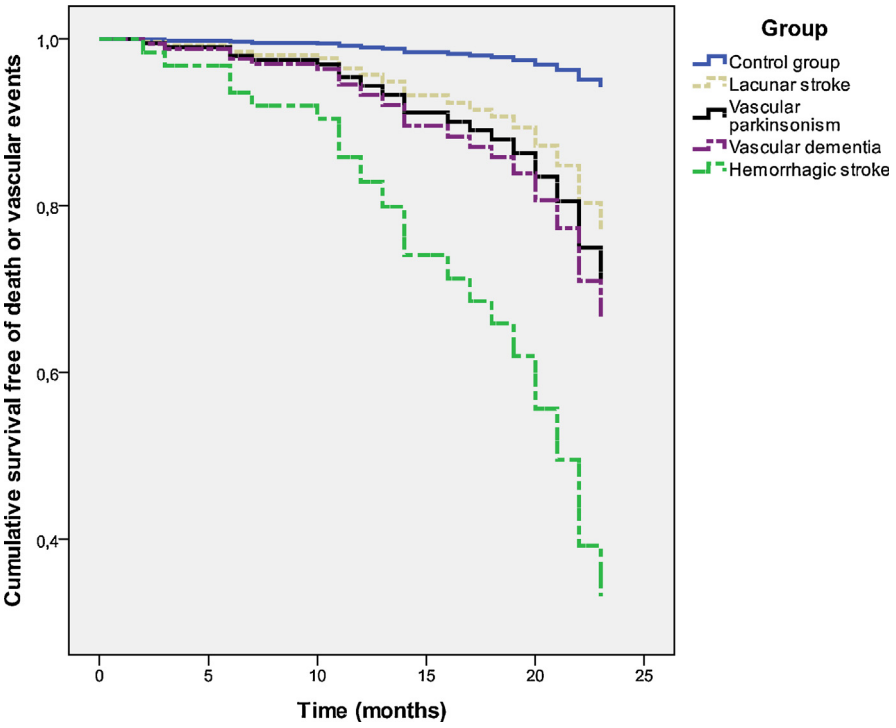

Fig. 1. Kaplan-Meier curves for all-cause mortality and non fatal vascular events by grouped diagnostic category (log rank, $p < 0.01$).

were present at baseline MRI. Recurrent symptomatic strokes (both ischemic and hemorrhagic) were observed in 17% of patients with CSVD during a two-year observation. Ischemic strokes were responsible for 61% of all vascular events in CSVD group, being the most frequent in patients presenting with VaD and HS. The long-term course of primary non-disabling hemorrhagic strokes or vascular dementia was in general unfavorable as 65% of patients with HS and 34% with VaD died or experienced recurrent vascular events during follow-up. We believe

Table 3. Sensitivity analyses in subsets of patients for main outcome, ischemic stroke and myocardial infarction.

	n (%)	Main outcome	Non-fatal IS	Non-fatal MI
All patients	205 (100)	4.56 (1.3–14.9)	9.73 (1.3–72.4)	0.66 0.1–3.9)
Excluding VaD, VaP	127 (62)	4.70 (1.3–16.2)	7.2 (0.89–57.8)	1.0 (0.13–7.2)
Excluding HS and LS	133 (64.8)	4.59 (1.3–15.7)	12.6 (1.6–97.3)	0.4 (0.3–4.5)
Excluding Grade 1 WMLs	182 (88.7)	5.12 (1.5–16.8)	10.9 (1.4–81.6)	0.57 (0.8–4.1)

VaP – vascular parkinsonism; VaD – vascular dementia; WMLs – white matter lesions; IS – ischemic stroke.

MI – myocardial infarction.

Values represent age and sex-adjusted HRs (95% CIs) for patients with cerebral small vessel disease vs controls.

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that, this excess risk in HS and LS groups was probably not linked with primary, qualifying event as the survival curves showed the highest incidence of events following the first year of observation. Exclusion of patients with atrial fibrillation and significant stenosis of extracranial or intracranial arteries in all patients resulted in a low incidence of thromboembolic events. Although patients with CSVD more frequently than CG had diabetes mellitus 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 (van Harten et al., 2007). Advanced white matter injury was also frequently found in patients with diabetes with CKD (Palacio et al., 2014).

In comparison to strokes of different ethiologes, lacunar and hemorrhagic strokes in patients with CSVD were regarded in the past as less debilitating due to the smaller dimensions of brain lesions (Poggesi et al., 2014). This view has been modified during the last decade when an excess of death and stroke recurrence has been consistently documented (Norrving, 2003). Previous studies showed that the risk of death immediately after the onset of lacunar stroke was low but increased with time reaching 10–15% between 5 and 10 years and 60% of the patients died after 10 years (Eriksson and Olsson, 2001). In our cohort, the 2-year case-fatality rate in patients with LS was lower (3.8%) compared to previously reported data (8–15%) but the risk of recurrent stroke (9.6%) or other vascular events (7.3%) was similar to rates of 5–11% reported in prior prospective and epidemiological studies (Kolominsky-Rabas et al., 2001; Jackson and Sudlow, 2005). Also SPS3 trial showed that depending on the blood pressure control, patients with recent LS experienced 8% to 10% of recurrent strokes and 6.6%-7% died during 3.7 years of follow up (The SPS3 Study Group, 2013). It gave an annualized rate of recurrent stroke between 2.25% and 2.77% and death from all causes between 1.74%-1.8%. SPS3 trial also demonstrated, that patients with diabetes were almost twice as likely to have a recurrent, disabling or fatal stroke, MI or death compared with patients without diabetes (Palacio et al., 2014).

Patients with HS characterized by the highest risk of death and vascular events. Overall 24-month case fatality rate was 45% what stood in concordance with previous reports, in which at 3 months 18%-33.5% patients with nontraumatic, primary intracranial hemorrhage (ICH) died and less than half of them survived up to 1 year (Al-Khaled and Eggers, 2014; Hemphill et al., 2009). In the metanalysis of the studies, the median 1-year mortality was 54.7% (range 46.0–63.6%) but these studies did not differentiate CSVD-related ICH from other causes (van Asch et al., 2010). Data pertaining to the risk of recurrent vascular events following ICH are scarce (Tveiten et al., 2013). In our cohort, 20% of patients with index HS experienced recurrent strokes, and that risk was higher than previously reported in unselected ICH patients (12% at 3 years) but the number of cases in presented

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study was small (Zia et al., 2009). More unfavorable course in our patients could be related to CSVD alone which is an independent predictor of worse outcomes in patients after spontaneous ICH (Caprio et al., 2013). We confirmed that the presence of severe WMLs is associated with a worse prognosis in terms of vascular events and death which is in concordance with the INTERACT2 study which showed that WMLs were linked with poor outcomes in acute ICH at 90 days (Sato et al., 2016). Meta-analysis and systematic review of 46 prospective studies revealed the doubled risk of death among patients with WMLs in comparison to those without (Debette and Markus, 2010). In a series of cohort studies based on the community-dwelling general population, the extent of WMLs increased also the risk of IS, myocardial infarction, and mortality. The reason is unclear because it is still difficult to make a precise distinction between the direct effects of CSVD markers and bystander phenomena from shared vascular risk factors causing systemic micro- and macroangiopathies (Yamauchi et al., 2002). We assessed the extent of WMLs solely, but there are other neuroimaging markers of cerebral CSVD, including cerebral MBs which represent poor prognostic markers of recurrent vascular events and functional recovery for stroke survivors (Kim and Lee, 2015; Charidimou et al., 2013).

Little is known about natural course of VaP and VaD caused by CSVD, which makes our data the more important. We demonstrated that patients with VaD and VaP had higher risk of main outcome or ischemic stroke comparing to CG, with a rate of all cause death of 9%. It was lower comparing to a study in which 24% individuals with VaD followed for 2 years died (van de Vorst et al., 2016). The higher risk of death and a greater risk of stroke and death from coronary events in that population probably resulted from an older age of population studied. Although VaD and VaP are not acute life-threatening disorders, our study documented a more unfavorable course in all clinical manifestations including chronic CSVD in which high risk of all-cause death and vascular events was demonstrated (HRs 4.59) compared to controls. An even more pronounced risk (relative risk 11.1) was reported previously when patients with different types of dementia were compared with controls, which may be, however attributed to their significantly older age (mean 85 years) than in current study (Chamandy and Wolfson, 2005). Although Parkinson's disease has been consistently reported to be associated with a higher risk of all-cause mortality and stroke in various epidemiologic studies, previous studies of VaP were conducted on small groups probably due to imprecise diagnostic criteria (Morgante et al., 2000). In one prospective follow-up study of an unselected incident cohort of patients with VaP (n = 38) and age-sex matched controls (n = 262), patients with VaP had increased mortality (HR 6.85) and 96% rate of death or dependency at 3 years (Fielding et al., 2016). The excess in the risk of nonvascular death in chronic CSVD can be explained. As these diseases progress patients become

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increasingly frail, which gives rise to complications like swallowing impairment, incontinence or falls.

It is interesting that even in the present study an apparent similarity emerged between the course of acute and chronic CSVD. Also all recurrent IS were of lacunar type what can further prove common pathogenetic mechanisms of these entities. Although an obviously different disease course in patients with CSVD and those with CG suggest pathophysiology of CSVD may be independent from that of atherosclerotic large artery disease, we found no significant difference in risk of MI in patients with CSVD (2%) and CG (3.6%). This could be related to previously undiagnosed CAD in CSVD group as systematic evaluation of CAD is not currently recommended in asymptomatic patients with a recent stroke. However, CAD events are common in patients who have had an ischemic stroke. Compared with the general population, stroke patients have an increased risk of death that notably results from MI. Yamamoto et al. reported that 3.3% patients experienced MI following lacunar infarct (Yamamoto et al., 2002). A systematic review and meta-analysis of 39 studies included 66.000 patients and showed the annual risk of either MI or nonstroke vascular death of approximately 2% for each outcome (Touzé et al., 2005). Although evidence supports the use of antiplatelet agents for preventing further infarction in patients with IS relating to CSVD, however there is still no good evidence that these drugs are effective in treating patients with VaD or VaP but in a routine clinical practice patients with clinically and radiologically documented CSVD usually receive aspirin in the secondary prevention of cerebrovascular disease. On the other hand there is increasing concern that antiplatelet treatment is associated with increased risk of cerebral haemorrhages in patients with extensive CSVD. Although patients with a recent stroke are at high risk for CAD, it is controversial whether stroke is an independent risk factor beyond classic risk factors e.g. hypertension, hypercholesterolemia or diabetes. According to the SPARCL Study which showed that treatment with statin reduced recurrent stroke and non-stroke-related vascular events in patients with a recent stroke, patients with IS should be considered to be a coronary risk equivalent with a prognosis similar to that of a patient with coronary artery disease (Amarenco et al., 2007). An AHA/ASA statement has recommended individual risk assessment based on risk scores, but there is no reliable method to estimate the risk of MI or vascular death after cerebrovascular events especially related to CSVD (Adams et al., 2003).

The results from our study suggest that regardless of the clinical manifestation, the course of CSVD is generally poor. It would be important for clinicians to identify high risk patients, and especially those with chronic CSVD, to implement more effective preventive strategies and to intensify cardiovascular risk factor management. Our findings also support the use of MRI beyond the classic stroke risk factors assessment as a possible tool for better identifying people with CSVD

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at high risk of stroke and other vascular events. Unfavorable course of CSVD may be attributable to either the poor control or the aftermath of traditional vascular risk factors but the association between CSVD and clinical outcome can depend upon other several underlying mechanisms. Cerebral small vessel disease reflects potential fragility of the brain and an increased susceptibility to ischemic or hemorrhagic brain damage. These changes may increase the risk of not only overt infarction from vessel occlusion but also chronic ischemia from reductions in perfusion and gas transfer in the white matter and deep brain structures (Arsava et al., 2009). It has been suggested that areas with extensive WMLs may be poorly supplied by collateral compensation, which may lead to IS extension, poor brain compensation and recovery (Grefkes et al., 2008).

Our study strengths include its prospective design and parallel 24 month observation of patients with well characterized different CSVD manifestations including rarely studied chronic VaP and VaD compared with control population sharing similar risk factors. Furthermore, CG was a random sample of the CSVD free population with high atherothrombotic risk that attended the same Outpatient Department at approximately the same time as CSVD group, which is a design that minimizes the potential for selection bias and confounding. Another advantage is the complete follow-up for mortality, and single-center design which allowed us to consistently collect all measures. Our study has also some limitations. The major weakness is the small number of patients and controls included which decreased the power of our study in detecting some significant differences among different groups. However this is also a limiting factor in most published reports on the subject. The total number of outcome events was relatively small what might have produced biased estimates and the results may not be generalizable to other population. Patients with VaP and VaD included in the present study were in an advanced stage of their disease therefore it remains unknown whether our results can be applied to less severely affected patient. The overall study period (24 months) could ideally have been longer to reach more significant results. As it is impossible to achieve a 100-percent accuracy in intravital diagnosis of parkinsonism without pathological confirmation, there may be in our study, as well as in any previous ones, some imprecision in that matter despite the fact that we applied strict diagnostic criteria based on all available clinical data. Future studies are needed to develop a predictive risk score for chronic CSVD manifestations, and to clarify the interaction between degenerative and vascular processes in their development.

6. Conclusions

The main outcome of our study is that, patients with CSVD have an excess risk of death and increased rate of lacunar stroke in comparison with controls with high atherothrombotic risk free of cerebrovascular disease. The study demonstrated that

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different clinical manifestations in CSVD, both acute or chronic have similar unfavorable prognosis in the 24 month of observation. The precise mechanisms by which CSVD mediates poor outcomes are unclear and require additional investigations. Further studies are warranted to evaluate the risk of CSVD in the long run.

Declarations

Author contribution statement

Jacek Staszewski: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Renata Piusińska-Macoch, Bogdan Brodacki, Ewa Skrobowska, Katarzyna Macek, Adam Stępień: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data.

Competing interest statement

The authors declare no conflict of interest.

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Additional information

No additional information is available for this paper.

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