



Clinical characterization of symptomatic microangiopathic brain lesions

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Background: Microangiopathic brain lesions can be separated in diffuse lesions – leukoaraiosis – and focal lesions – lacunes. Leukoaraiosis and lacunes are caused by common cerebrovascular risk factors, but whether they represent a common entity is not sufficiently investigated. The present study aimed to determine the clinical profiles associated with the extent of leukoaraiosis and lacunes. **Methods:** Sixty-four consecutive patients with acute microangiopathic stroke were studied. Leukoaraiosis and lacunes were stratified according to their MRI-based extent. Standardized clinical assessment included clinical syndromes, cerebrovascular risk factors, cognitive performance, retinal imaging, ultrasonography, blood, and urine parameters. **Results:** Different clinical profiles for leukoaraiosis and lacunes were found. Regarding leukoaraiosis, the cognitive scores (SISCO, mini mental score examination, mental examination) and the presence of hyperlipidemia decreased as the severity of leukoaraiosis increased. Univariate and multivariate analysis revealed that these cognitive score values as well as the presence of hyperlipidemia correlated significantly with no or only mild leukoaraiosis. Regarding lacunes, the percentage of migraine, previous stroke events, hydrocephalus, left ventricular hypertrophy, and a higher National Institutes of Health Stroke Scale increased as the number of lacunar lesions increased. Statistical analysis revealed that these parameters correlated not significantly with the number of lacunes. **Conclusions:** The findings suggests that leukoaraiosis and lacunes are different microangiopathic entities potentially requiring different treatment concepts.

Keywords: microangiopathic brain lesions, leukoaraiosis, lacunar lesion, cardiovascular risk factor

INTRODUCTION

Symptomatic microangiopathic brain lesions (MBL) constitute about one quarter of all ischemic strokes and are a leading cause of morbidity and mortality (Lammie, 2002). Morphologically, diffuse affection of cerebral white matter, i.e., – leukoaraiosis – and focal lesions – lacunes – are distinguished (Barkhof and Scheltens, 2002; Pantoni et al., 2002; Pantoni, 2010).

Previous population-based studies investigated a variety of clinical factors in the context of MBL. These were associated with arterial hypertension, diabetes mellitus, and hyperlipidemia (Hachinski et al., 1987; Sander et al., 2000; Wong et al., 2002). It is generally assumed that leukoaraiosis and lacunar lesions share common risk factors. However, few studies have conducted a clinical profile analysis of the two entities in a single study design (Kim et al., 2011).

The present study aimed to determine differences in the clinical profile between leukoaraiosis and lacunar lesions. In microangiopathic stroke patients, the associations and coincidence

of specific clinical parameters regarding the extent of MBL were investigated.

MATERIALS AND METHODS

STUDY POPULATION

Consecutive patients with microangiopathic stroke who were admitted to our stroke unit during a 6-months recruiting period were prospectively enrolled. Inclusion criteria was a clinically defined lacunar syndrome according to published criteria (Fisher, 1965; Mohr and Marti-Vilalta, 1998). Exclusion criteria were cortical symptoms, hemorrhagic stroke, or large vessel stroke. The study was approved by the local ethics committee.

MRI SCANNING

The MRI protocol comprised T2 weighted images, T2*-weighted images, diffusion-weighted images, and dark fluid sequences (Siemens 5; 1.5 T) in 6 mm slices from the vertex to the foramen magnum. Images were evaluated by two independent blinded

observers (a senior neuroradiologist and an experienced stroke neurologist).

MICROANGIOPATHIC BRAIN LESIONS

Leukoaraiosis was defined according to published criteria (Pantoni et al., 2002; Pantoni, 2010). Subjects with discrete leukoaraiosis were not considered to be affected (Hachinski et al., 1987; Barkhof and Scheltens, 2002; Pantoni et al., 2002). The extent of leukoaraiosis was divided into mild, moderate, and severe changes (Blennow et al., 1991; Pantoni et al., 2002). Lacunar lesions were defined as lesions with a diameter of 6–15 mm in typical locations. The number of lacunar lesions was classified into single, two to five and more than five lacunar lesions (Wahlund et al., 2001).

CEREBROVASCULAR RISK FACTORS

Diagnostic work up included a *standardized questionnaire* evaluating history of cardiovascular diseases including myocardial infarction (MI), coronary artery disease (CAD), previous stroke, and family history. On admission, the leading clinical symptoms, the *National Institutes of Health Stroke Scale* (NIHSS), *Rankin Scale* (RS), and *Barthel Index* (BI) were documented. All other clinical data were recorded 7 days after the acute stroke event. *Arterial hypertension* was defined by either repeated elevated systolic blood pressure >160 and/or diastolic blood pressure >95 (Carter, 2004) or the previous use of antihypertensive drugs. *Diabetes* was defined by either HbA1c $\geq 6\%$ or use of antidiabetics (Peters et al., 1996). *Hyperlipidemia* was defined either by total cholesterol ≥ 6.5 mmol/l, triglycerides ≥ 2.3 , HDL cholesterol ≤ 1.0 mmol/l, or use of lipid-lowering drugs. *Proteinuria* was defined as urinary albumin >20 mg/dl. *Renal insufficiency* was defined as serum creatinine >120 $\mu\text{mol/l}$. Patients who did not currently *smoke* were divided in non-smokers and past smokers (≥ 5 years). Current smokers were evaluated in pack years (py). *Alcohol consumption* was stratified into g alcohol/month (Vriz et al., 1998). *Body mass index* (BMI, kg/m^2) was calculated from height and weight measurements.

COGNITIVE FUNCTIONS

Cognitive functions were assessed by the *SIDAM score SISCO* (Structured Interview for the Diagnosis of Dementia of the Alzheimer Type, multi-infarct dementia, and dementias of other etiology according to DSM-III-R and ICD-10) including the *SIDAM Mini Mental Score Examination* (MMSE) and *mental examination* (ME; Zaudig, 1992). In addition, the *Beck Depression Inventory* was performed (Beck et al., 1961).

RETINAL IMAGING

Retinal imaging to evaluate hypertensive retinopathy was performed after 5 min dark adaptation in mydriatic pupils. An ophthalmologist who was unaware of the clinical data evaluated the retinal imaging according to a standardized protocol. Hypertensive retinopathy was classified in mild, moderate, and severe retinopathy (Wong et al., 2002; Wong, 2004).

VASCULAR ULTRASONOGRAPHY

The *pulsatility index* (PI) of the MCA was recorded with a Doppler device (Multi-Dop X4, DWL) with the PI calculated automatically.

Intima-media-thickness of the common carotid artery was defined by duplex sonography according to the method described by Simons et al. (1999).

ELECTROCARDIOGRAPHY

Left ventricular hypertrophy (LVH) was identified by the gender specific Cornell voltage-duration product $(\text{RaVL} + \text{SV}_{\text{III}}) \times \text{QRS} > 2440$ mm·ms in men and $(\text{RaVL} + \text{SV}_{\text{III}} + 8\text{mm}) \times \text{QRS} > 2440$ mm·ms in women. An additional acceptance criterion was based on the non-gender-specific Sokolow–Lyon voltage combination $(\text{SV}_1 + \text{RV}_5 \text{ or } \text{RV}_6) > 38$ mm (Dahlof et al., 1998). *Atrial fibrillation* was also defined by either conventional electrocardiogram or history of atrial fibrillation.

DATA ANALYSIS

Data were presented as mean \pm SD for continuous variables and as proportions for categorical variables. Exploratory data analysis was performed to explore possible associations and to generate hypotheses. Due to the small number of patients, unadjusted *p*-values from Fisher's exact tests are reported only to give a hint on possible associations. Due to the small sample size, variables leukoaraiosis and lacunar lesions were dichotomized to at least ensure useful group sizes for group comparisons: leukoaraiosis was dichotomized by either non or only mild changes on MRI, or moderate to severe leukoaraiosis and lacunes were dichotomized by either no or one lacunar lesion, or ≥ 2 lacunes.

RESULTS

Sixty-four patients (25 female, 35 male, mean age of 65.5 ± 10.8 years) were investigated. Baseline characteristics of the study population are given in the **Table 1**.

LEUKOARAIOSIS

Using four groups (no, mild, moderate, and severe leukoaraiosis) for evaluation of mean values, we observed that the cognitive scores SISCO, ME, and MMSE as well as the percentage of patients with hyperlipidemia decreased as the severity of leukoaraiosis increased. Using two groups (non or mild leukoaraiosis versus moderate or severe leukoaraiosis) for statistical analysis, Fisher's exact test revealed that the cognitive score values for ME, MME, and SISCO above median correlated significantly with no or mild leukoaraiosis. The same was found for the percentage of patients with hyperlipidemia.

Due to the small sample size using multivariable methods is a problematical issue. To inspect the joint influence of the risk factors detected by univariate analysis on the probability for at least moderate leukoaraiosis and to adjust for age, small logistic regression models were selected and fitted corresponding to the following criteria: as few as possible missing observations, significant exploratory variables, goodness of fit (calibration, Hosmer–Lemeshow-Test), usefulness at prediction of outcome (Nagelkerke R^2), and ability for discrimination (AUCROC). Only models with age and two additional exploratory variables were incorporated. With the caveat of small sample size and therefore purely empirical selection of models there were two “best” selected models which roughly complied with the criteria above (**Table 2**).

Table 1 | Clinical parameters in regard to the extent of cerebral microangiopathy.

Parameter (n)	Leukoaraiosis	Leukoaraiosis	Lacunae	Lacunae
	No + mild (48)	Moderate + severe (16)	0 + 1 (14)	2–5 + > 5 (50)
Mean age (years), \pm SD	63 \pm 11	68 \pm 9	65 \pm 9	64 \pm 11
Lacunar lesions, % (n)	83 (40)	100 (16)		
Leukoaraiosis, % (n)			57 (8)	82 (41)
SISCO, mean \pm SD	50 \pm 4	44 \pm 9	49 \pm 5	48 \pm 7
MME, mean \pm SD	28 \pm 2	26 \pm 4	28 \pm 2	28 \pm 3
ME, mean \pm SD	17 \pm 3	13 \pm 3	16 \pm 3	16 \pm 3
Hyperlipidemia (history), % (n)	54 (26)	19 (3)	64 (9)	40 (20)
Hyperlipidemia (measurements), % (n)	71 (34)	56 (9)	71 (10)	66 (33)
Migraine, % (n)	29 (14)	38 (6)	14 (2)	36 (18)
Previous stroke (history), % (n)	25 (12)	56 (9)	7 (1)	40 (20)
Previous stroke (imaging), % (n)	75 (36)	100 (16)	14 (2)	100 (50)
Left ventricular hypertrophy, % (n)	6 (3)	6 (1)	0 (0)	8 (4)
Hydrocephalus, % (n)	2 (1)	19 (3)	0 (0)	8 (4)
NIHSS, mean \pm SD	3.4 \pm 1.8	3.8 \pm 2.0	3.0 \pm 2.3	3.6 \pm 1.7
Barthel index, mean \pm SD	92.5 \pm 17.8	89.7 \pm 22.3	91.8 \pm 25.2	91.8 \pm 17.1
Rankin scale, mean \pm SD	2.2 \pm 1.2	2.3 \pm 1.3	2.1 \pm 1.2	2.2 \pm 1.2
Retinopathy, % (n)	48 (23)	75 (12)	43 (6)	58 (29)
Hypertension (history), % (n)	71 (34)	69 (11)	86 (12)	66 (33)
Hypertension (measurements), % (n)	73 (35)	75 (12)	86 (12)	70 (35)
Diabetes (history), % (n)	29 (14)	31 (5)	21 (3)	32 (16)
Diabetes (measurements), % (n)	40 (19)	50 (8)	36 (5)	44 (22)
Pack years, mean \pm SD	22 \pm 31	9 \pm 11	13 \pm 17	21 \pm 30
Current smoking, n (%)	38 (18)	31 (5)	21 (3)	40 (20)
Alcohol (g/month), mean \pm SD	259 \pm 532	154 \pm 354	229 \pm 449	299 \pm 509
BMI, mean \pm SD	27 \pm 5	26 \pm 4	27 \pm 5	27 \pm 4
Atrial fibrillation, % (n)	13 (6)	13 (2)	21 (3)	10 (5)
Foramen ovale, % (n)	13 (6)	6 (1)	14 (2)	10 (5)
Pulsatility index, mean \pm SD	1.06 \pm 0.20	1.15 \pm 0.19	1.03 \pm 0.13	1.10 \pm 0.21
Intima-media thickness, mean \pm SD	0.08 \pm 0.02	0.08 \pm 0.01	0.08 \pm 0.02	0.10 \pm 0.01
Proteinuria, % (n)	15 (7)	6 (1)	7 (1)	14 (7)
Emotional incontinence, % (n)	6 (3)	19 (3)	14 (2)	8 (4)
BDI, mean \pm SD	8 \pm 6	10 \pm 7	7 \pm 5	8 \pm 6

LACUNAR LESIONS

Using four groups (no, single, two to five, and >5 lacunar lesion) for evaluation of mean values, the percentage of migraine, previous stroke events, hydrocephalus, LVH, and a higher NIHSS increased as the number of lacunar lesions increased. Using two groups (no or one lacunar lesion versus ≥ 2 lacunar lesions) for statistical analysis, univariate analysis (for continuous variables: Man–Whitney test; for categorical variables: Fisher's exact test) revealed no significantly associated clinical parameters even at significance level 0.10. Therefore in view of only 14 patients with less than two lacunar lesions multivariate analysis was not performed.

DISCUSSION

The pathogenesis of MBL is poorly understood. It remains unclear why some patients develop isolated lacunae while other patients also develop leukoaraiosis (Hassan et al., 2003). Hypertension is a major risk factor but fails to account for much of the risk

(Boiten et al., 1993; Hassan et al., 2003). Imaging and autopsy-based studies propose two types of MBL. They separate patients with single lacunae without leukoaraiosis, a microatheromatous disease of larger perforating arteries, and the usual vascular risk factors versus patients with multiple lacunae and leukoaraiosis, diffuse arteriosclerosis of smaller perforating arteries, and a high frequency of hypertension (Fisher, 1969; Boiten et al., 1993; Khan et al., 2007).

Only few studies analyzed the two entities of MBL in a single study design. The present study investigated a variety of clinical parameters with regard to the extent of leukoaraiosis and lacunae. The study results demonstrated evidence for different clinical profiles in leukoaraiosis and lacunae, respectively.

The most reliable parameter regarding the severity of leukoaraiosis was the cognitive performance measured with the SIDAM including the SISCO, MMSE, and ME. The SIDAM test covers a broad range of cognitive functions for diagnosis of even mild cognitive impairment (Zaudig, 1992). Even the

Table 2 | Statistical analysis (dichotomization in no leukoaraiosis + mild leukoaraiosis versus moderate leukoaraiosis + severe leukoaraiosis).

UNIVARIATE ANALYSIS, ME, SISCO, AND MMS DICHOTOMIZED ACCORDING TO SAMPLE MEDIAN				
Original variable	Median	p-Value [§]	OR	95% CI for OR
ME	16	<0.0005	0.05	(0.01, 0.38)
SISCO	50	0.001	0.05	(0.01, 0.41)
MMS	28	0.008	0.16	(0.04, 0.65)
Hyperlipidemia		0.020	0.19	(0.05, 0.77)
MULTIVARIATE ANALYSIS USING FORWARD SELECTION (WALD-TEST)				
Variable		p-Value wald-test	OR	95% CI OR
Model 1				
Age		0.500	0.97	(0.90, 1.05)
ME		0.005	0.03	(0.003, 0.36)
Hyperlipidemia		0.030	0.17	(0.03, 0.84)
Model 2				
Age		0.439	0.97	(0.90, 1.05)
SISCO		0.003	0.02	(0.002, 0.28)
Hyperlipidemia		0.007	0.10	(0.02, 0.52)

[§]p-Values from Fisher's exact test.

CI, Confidence Interval; OR, Odds Ratio.

subitems MMSE and ME were sufficient to indicate at least moderate leukoaraiosis. Consistently, other MRI-based studies found that the extent of leukoaraiosis is strongly correlated with cognitive performance (Merino, 2008) and that the progression of leukoaraiosis is associated with progression in cognitive decline (Dijk et al., 2008). Interestingly, the presence of hyperlipidemia was a negative indicator of leukoaraiosis. Some authors suggest a protective role of hyperlipidemia against cerebral small-vessel disease (Warsch and Wright, 2010). Since 96% of our patients with known hyperlipidemia used statins, pharmacological effects have also to be considered.

Regarding the extent of lacunes, a higher NIHSS, previous stroke events, and LVH were more present in patients with multiple

lacunes, but no statistical significance was found. Interestingly, the presence of migraine was higher in patients with multiple lacunes. Migraine is a leading clinical feature in some monogenetic small-vessel diseases such CADASIL or HERNs (Dichgans et al., 1998; Kruit et al., 2004). The etiology of MBL associated with migraine is unknown (Kruit et al., 2004). Spreading depolarizations are assumed to be the pathophysiological correlate of the migraine (Moskowitz, 2007). Small-vessel disease of the brain likely causes recurrent small perfusion deficits that might give rise to spreading depolarizations and migraine, consecutively (Dreier et al., 2002).

Arterial hypertension and older age were found in the vast majority of patients with leukoaraiosis and lacunes, as shown in other studies (de Leeuw et al., 2002). This validates arterial hypertension as an important risk factor for leukoaraiosis and lacunar lesions (Bryan et al., 1997; Lee et al., 2000). However, a correlation with the severity of MBL was not found. 25% of the study cohort had no hypertension, indicating that MBL are not synonymous with hypertensive microangiopathy.

The limiting factor of the present study is the small number of patients due to the intraindividually extraordinary expense for conducting a broad and general investigation. Follow up studies have to confirm the assumption of different microangiopathic entities. As a drawback of the MR protocol- the smallest lacunar lesions with a diameter of 5–6 mm might have been missed.

In conclusion, only few studies separately investigated leukoaraiosis and lacunar lesions. The present study found different clinical profiles of patients with leukoaraiosis and lacunes. This suggests that the pathophysiological process is likely to differ and different treatment concepts may be required (Khan et al., 2007).

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