J Neural Transm (2007) [Suppl 72]: 181–188

Printed in Austria

Journal of Neural Transmission

VITA study: white matter hyperintensities of vascular and degenerative origin in the elderly

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Summary The etiology of white matter hyperintensities (WMH) seen on T2-weighted cranial magnetic resonance images is a matter of debate. We investigated deep and periventricular WMH in the brains of a community-based cohort of 532 subjects aged 75–76 years. The objective of this study was to determine whether WMH at age of 75 years were associated rather with vascular factors than with degenerative factors.

Arterial hypertension treated with antihypertensive drugs favored WMH, and WMH were found more frequently in subjects with focal vascular lesions. Additionally, we found significant associations between both, deep white matter and periventricular hyperintensities, and focal atrophy of medial temporal lobe structures. The odds ratio for deep WMH in subjects with more severe medial temporal atrophy was 4.4 (95%-CI: 1.9–9.8) that for periventricular hyperintensities was 3.9 (95%-CI: 1.7–8.8).

These findings might indicate that not only vascular factors alone but also degenerative factors favor the occurrence of WMH after the age of 75 years.

Keywords: White matter hyperintensities, Alzheimer dementia, vascular lesions, medial temporal lobe atrophy

Introduction

White matter hyperintensities (WMH) on T2-weighted cranial magnetic resonance images (MRI) are common in the brains of elderly people, and their frequency increases strongly with age (Fazekas et al., 1987; Christiansen et al., 1994; Longstreth et al., 1996). The etiology of WMH is still a matter of debate. They are interpreted as a consequence of chronic cerebral hypoperfusion, favor a clinical diagnosis of ''subcortical vascular encephalopathy'', and they are seen as a significant part of the pathophysiology of vascular cognitive impairment (Breteler et al., 1994b; Liao et al., 1996; Longstreth et al., 1996; Pantoni et al., 1996; Pantoni, 2002; De Leeuw et al., 1999; O'Brien et al., 2003). Patients with such abnormalities are described as being more likely exposed to vascular risk factors and infarcts (Schmidt et al., 1992, 1999; Breteler et al., 1994b; Lindgren et al., 1994; Fukuda and Kitani, 1995; Ylikoski et al., 1995; Liao et al., 1996; Longstreth et al., 1996; De Leeuw et al., 1999; Vermeer et al., 2002; Streifler et al., 2003).

WMH were found to be more severe in subjects with a diagnosis of Alzheimer dementia (AD) where these lesions are not necessarily associated with hypertensive vascular changes (Brun and Englund, 1986; Breteler et al., 1994b; De Groot et al., 2000). The few existing clinico-pathological case-reports describe a non-ischemic nature of a certain proportion of WMH, but most of these clinico-pathological cases had died at an age younger than 75 years (Janota et al., 1989; Chimowitz et al., 1992; Fazekas et al., 1993; Thomas et al., 2002; Ukada et al., 2002).

We investigated WMH in the brains of a large community-based population of 75–76 years of age. We report the frequency of both, deep white matter hyperintensities (DWMH) and periventricular hyperintensities (PVH). We calculated the impact of various vascular risk factors, and of cerebral infarcts on both, DWMH and PVH, and compared

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these effects with the impact of medial temporal lobe atrophy. The question posed was whether DWMH and PVH at an age of 75 years were associated rather with vascular factors than with degenerative factors, as medial temporal lobe atrophy has been shown to characterize AD (Scheltens et al., 1992, 1995b, 1997; Wahlund et al., 2000; Petersen et al., 2000).

Subjects and methods

The VITA study is a prospective longitudinal study on mental aging. The study design, recruitment strategy and participation rate have been described: at baseline the study tried to investigate every 75-year old inhabitant of a geographically defined area of Vienna, which lies on the left shore of the Danube (''Vienna Transdanube''), born between May 1925 and June 1926 (Fischer et al., 2002). This area consists of two districts (21st and 22nd districts of Vienna) with 264.672 inhabitants. We invited all individuals of this geographical birth-cohort to participate in the study (institutionalized and non-institutionalized).

The main aim of the VITA is the prediction of incident cases of dementia after 30 months and after 60 months. Because age is the strongest predictor of cognitive decline in the elderly, the variance of age was minimized in the VITA and subjects were invited to participate in the sequence of their birth, which means that older subjects of the cohort were seen earlier. With the help of a liberal recruitment strategy, which had been accepted by the local ethics commission, 1505 inhabitants were contacted. The participation rate was 46% (telephone interview or short investigation or complete investigation). The standard deviation of age in the 606 subjects (40.3% of the 1505) who underwent the complete investigation was only 0.4 years. The complete investigation comprised medical and psychosocial interviews, psychological tests, psychiatric and neurological scales, blood characteristic, and a cranial MRI (Fischer et al., 2002). It lasted about 9 hours per patient (contact session including informed consent; some days later: main session including MRI; 2 weeks later: discussion of results with the participant).

The basal population seen between 2000 and 2002 consisted of 606 individuals, who underwent all investigations including blood sampling. Exclusion criteria for MRI were conventional: 1) presence of a cardiac pacemaker, some types of valvular prothesis, or other internal electrical device; 2) history of neurosurgery or aneurysm before 1985; and 3) presence of metal fragments in the eyes, brain, or spinal cord. Cranial MRI could be carried out in 532 of the 606 participants. VITA participants without MRI did not differ from those with MRI as far as vascular risk factors, history of stroke, history of cardiovascular disease, and cognitive scores are concerned. The MRI investigation was performed using a 1.0 Tesla unit (Siemens Impact Expert) with a circular polarized skull coil. The following sequences were obtained: transverse PD and T2-weighted TSE, coronary T1-weighted gradient echo sequence (MPRAGE) and a thin-section IR sequence in the olfactory region. Lacunes (i.e. small infarcts) were defined as cyst-like lesions with signal-intensity isotense to cerebrospinal fluid on both, T1 and T2 measurements, and a maximum diameter of 15 mm. Lesions of more than 15 mm in size that follow a vascular territory regardless of grey or white matter were rated as infarcts. For the rating of medial temporal lobe atrophy (MTA) the hippocampal area along the longitudinal axis of the hippocampus was reconstructed.

The presence and severity of WMH was determined by the Fazekas rating including a four point scale to assess PVH (0, absent; 1, caps or thin lining; 2, smooth halo; and 3, irregular areas extending into the deep white matter) and a four point scale to assess DWMH (0, absent; 1, large punctate foci; 2, beginning confluence of foci; and 3, large confluent areas) (Fazekas et al., 1987). Evaluation of various rating systems for WMH showed the superiority of this rating method concerning interrater reliability and also showed high validity compared with quantitative volumetric measurement of white matter changes (Kapeller et al., 2003). The MRIs of the first consecutive 105 subjects were assessed independently by two experienced radiologists. Inter-rater reliability for PVH and DWMH was high (PVH: Spearman $\rho = 0.621$; $p < 0.000$; DWMH: $\rho = 0.648$; $p < 0.000$). For statistical calculations only ratings of radiologist 1 (W.K.) were taken, who rated all 532 MRIs blind to all demographic, medical, neurological, psychiatric, and neuropsychological data.

Local atrophy of the medial temporal lobe (MTA) was assessed qualitatively on a 0–4 scale according to Scheltens et al. (1992, 1995b, 1997): scores range from 0 (no atrophy) to 4 (very severe atrophy), but 4 was not found in our community-based age-cohort. The rating scale was based on a visual estimation of both the volume of the medial temporal lobe, including the hippocampus proper, dentate gyrus, subiculum, and parahippocampal gyrus, and the volume of the surrounding cerebrospinal fluid spaces, in particular, the temporal horn of the lateral ventricle and the choroid fissure on both sides. This visual method of scoring correlates well with linear and volumetric measurements and has reasonably good inter- and intrarater reliability (Scheltens et al., 1995b, 1997; Kapeller et al., 2003). Comparisons between volumetric methods and visual rating

of MTA have shown no advantage for volumetry (Wahlund et al., 2000).

Vascular risk factors were described in the population of 532 subjects who completed the cranial MRI. We included the following vascular risk factors in orienting analyses of associations to WMH: HbA1c in serum; serum levels of low-density lipoprotein cholesterol (LDL), of high-density lipoprotein cholesterol (HDL), and of triglyzceride; lipoprotein (a) plasma level, homocysteine serum level; fibrinogen plasma level; C-reactive protein; body mass index; years of smoking; therapy with lipid-lowering drugs (no/yes); therapy with blood pressure lowering drugs (no/yes), systolic blood pressure (sBP), diastolic blood pressure (dBP). High blood pressure was defined as systolic blood pressure >135 mmHg or diastolic blood pressure >85 mmHg according to the seventh report of the joint national committee on high blood pressure (Chobanian et al., 2003). Subjects with high blood pressure after 5 min rest or those taking antihypertensive medication were considered ''hypertensives''. A tendency of orthostatic hypotension after standing motionless for 1 min following resting position (sitting or whenever possible supine for at least 10 min) was characterized by the difference of systolic blood pressure during rest minus the systolic blood pressure after 1-minute standing (Polinsky and Martin, 1994).

Statistical analyses (except ordinal regressions) were performed using the SPSS-11.5 Statistical Package for the Social Sciences. Group differences in categorical variables were analyzed by χ^2 tests. Spearman nonparametric correlations were calculated between each vascular risk factor on the one hand and DWMH or PVH on the other hand. Only correlations with a *p*-value lower than 0.15 were considered for further regression analysis. Stepwise ordinal regressions were performed to search for DWMH- and PVH-inducing risk factors using the DWMH scores (no–mild–moderate–severe) and PVH scores (no–mild–moderate–severe) as dependent variables and gender, BMI, vascular risk factors, and vascular or degenerative MRI findings as predictors. Vascular MRI findings were lacunes (i.e. small infarcts) or infarcts. The MRI finding possibly indicating degeneration was the visual rating of MTA. Vascular risk factors in the ordinal regressions were: HbA1c, LDL-cholesterol, HDL-cholesterol, triglyzcerides, fibrinogen, homocysteine, C-reactive protein, lipoprotein (a), sBP, dBP, smoking, lipid-lowering drugs (no/yes), and antihypertensives (no/yes). Then again, a stepwise ordinal regression was performed with all significant variables and their interactions. To reduce the number of missing observations, a fixed, non-stepwise model was then calculated with all significant variables. The probability of being in a higher category of white-matter lesions was modeled. The probability to enter or to stay in the model was set to 0.05. Ordinal regression analyses were done using SAS 8.

Results

Prevalence of DWMH and PVH in the VITA participants are shown in Table 1a.

DWMH were not rated because of a possible artifact in one male subject. A total of 31% (167 of 531) were free of any DWMH, 55% (290 of 532) did not show any PVH. WMH of any type or severity were found in 72% of subjects

Table 1a. *Vascular risk factors in patients with various degrees of deep WMH or periventricular hyperintensities*

Characteristics	DWMH				PVH			
	0	1	2	3	0	1	2	3
Total, *n*	167	194	111	59	290	167	17	58
Gender, m/f	74/93	81/113	35/76	23/36	116/174	63/104	9/8	26/32
Body mass index	27 (4)	27 (4)	27 (4)	28 (4)	27 (4)	27 (4)	29 (5)	27 (4)
HbA1c	5.8 (1)	6.0 (4)	6.0 (1)	6.0 (1)	6.0 (3)	6.0 (1)	6.0 (1)	6.0 (1)
LDL-cholesterol	148 (40)	141 (44)	143 (36)	143 (37)	149 (40)	146 (42)	160 (40)	140 (36)
HDL-cholesterol	58 (15)	60 (15)	61 (17)	56 (14)	59 (15)	59 (14)	60 (17)	59 (17)
Triglyzcerides	129 (59)	130 (64)	138 (63)	148 (78)	130 (62)	137 (71)	126 (42)	143 (59)
Fibrinogen	390 (82)	391 (91)	387 (87)	386 (91)	393 (91)	385 (79)	380 (69)	389 (94)
Homocysteine	14 (5)	14 (7)	14 (5)	15 (4)	114 (6)	14 (4)	17 (8)	15 (5)
C-reactive protein	5.1 (8.8)	4.8 (8.5)	3.6 (4.9)	4.6 (7.6)	5.2 (9.1)	3.5 (5.0)	3.2 (4.2)	4.7 (6.1)
Lipoprotein, Lp(a)	0.18 (0.17)	0.18 (0.18)	0.18 (0.17)	0.17 (0.12)	0.18 (0.18)	0.17 (0.18)	0.10 (0.02)	0.20 (0.12)
BP diastol, mmHg	81 (9)	83 (11)	81 (10)	84 (10)	82 (10)	82 (11)	87 (11)	81 (9)
BP systol, mmHg	145 (21)	148 (21)	145 (19)	147 (23)	146 (20)	147 (22)	155 (22)	142 (19)
Orthostatic hypotension	7.2 (16)	7.0 (18)	8.2 (15)	8.2 (17)	7.8 (17)	7.0 (17)	8.1 (23)	6.7 (14)
Smoking, % positive history	42	44	35	30	42	42	41	45
% on antihypertensive drugs	62	59	65	76	61	62	82	69
% on lipid-lowering drugs	22	19	23	25	19	23	24	26

Table 1b. *Vascular risk factors in patients without severe WMH compared to patients with both, severe DWMH and severe PVH (SD in brackets; p-values refer to t-tests or χ^2 test)*

	Neither severe DWMH nor severe PVH $n=351$	Both, severe DWMH and severe PVH $n=65$	p-Value
Gender, m/f*	150/201	30/35	0.609
Body Mass Index	27 (4)	28 (5)	0.203
HbA1c	6.0 (3.2)	5.8 (0.9)	0.619
LDL-cholesterol	150 (42)	143 (37)	0.208
HDL-cholesterol	59 (15)	59 (17)	0.850
Triglyzcerides	130 (61)	139 (54)	0.233
Fibrinogen	390 (88)	385 (93)	0.636
Homocysteine	14 (5.6)	15 (4.9)	0.143
C-reactive protein	5.0 (8.7)	4.4 (5.4)	0.637
Lipoprotein, Lp(a)	0.18 (0.18)	0.18 (0.12)	0.941
BP diastol, mmHg	82 (10)	82 (9)	0.835
BP systol, mmHg	147 (20)	144 (18)	0.270
Orthostatic hypotension	7.1 (17.2)	7.1 (16.5)	0.993
Smoking history *	43%	43%	0.993
Antihypertensives *	60%	74%	0.036
Lipid-lowering drugs*	19%	23%	0.501

* χ^2 test.

and 42% had both, DWMH and PVH of any severity. DWMH and PVH were highly intercorrelated (Spearman $\rho=0.658$; $p<0.0001$; $n=531$). No single subject had only confluent DWMH without PVH and no single subject had only irregular PVH without DWMH.

A comparison of the 351 patients with neither confluent DWMH nor confluent PVH with the 65 patients with both, confluent DWMH and PVH, concerning vascular risk factors showed only one significant comparison: patients with confluent white matter changes took antihypertensive drugs more frequently (Table 1b).

Each vascular risk factor was found in a high percentage of these 532 subjects: 68.6% had arterial hypertension at the time of the investigation measured after 10 min rest in sitting position; 62.8% are currently taking antihypertensives. We found elevated BP (>135/85) in 238 subjects, i.e. 71% of the 334 subjects who were taking antihypertensives. Taken together, 86.7% had either antihypertensive treatment and/or high blood pressure and could be labeled as ''hypertensives''.

A tendency to orthostatic hypotension is described by a postural fall of systolic blood pressure: 16.4% of the probands had a drop of systolic blood pressure of more than 20 mmHg. The drop in systolic blood pressure correlated significantly with a) systolic blood pressure ($\rho=0.305$; $p<0.0001$), b) diastolic blood pressure ($\rho=0.099$; $p=0.024$), and c) with the amplitude of blood pressure after 1 min standing motionless ($\rho=-0.372$; $p<0.0001$). The postural fall of systolic blood pressure was not associated with other vascular risk factors or any findings on MRI.

A positive history of smoking was found in 226 participants: 34.3% of the population had a history of at least 15 years of smoking, 10.7% had a history of smoking of at least 45 years. Diabetes mellitus was present in 80 subjects. Mean HbA1c of the entire cohort was 5.9% (sd = 2.6): 14.8% had values higher than 6.5 and 9.5% had values higher than 7.0%. Mean HDL-cholesterol was 59.1 mg/dl (sd = 15.2); 28.9% had HDL-cholesterol lower than 50 mg/dl. Mean LDL-cholesterol was 147.6 mg/dl (sd = 40.5); LDL-cholesterol was higher than 170 mg/dl in 28% of the cohort and higher than 200 mg/dl in 9.8% of the patients. Statines were given to 17.5% of the subjects (93 patients), other lipid-lowering drugs to 25 subjects (4.7%): 5 subjects took both – statines and other lipid-lowering drugs. Mean homocysteine blood level was 14.1 μmol/l (sd = 5.4): 30.6% had homocysteine levels higher than 15.0 μmol/l, 19.1% higher than 17.5 μmol/l. Homocysteine levels were highly correlated with both low folic acid serum levels ($r=-0.26$; $p=0.000$; $n=529$) and low serum vitamin B12 levels ($r=-0.24$; $p=0.000$; $n=528$). Lipoprotein (a) levels (mean 0.18 g/l, sd = 0.17) showed weak correlation with LDL-cholesterol levels ($\rho=0.183$; $p=0.021$).

MTA was found to be mild in 13%, moderate in 3.3% (20 subjects) and severe in 0.3% (2 subjects) of the probands. MTA could not be rated due to artifacts in 8 subjects. Lacunes or infarcts (diameter on MRI smaller or greater than 1.5 cm) were found in 100 out of 532 probands. MRI lacunes correlated significantly with MRI infarcts ($\rho=0.178$; $p<0.0001$). Lacunes without infarcts were found in 64 subjects, and 13 subjects showed lacunes together with greater infarcts.

Associations between vascular risk factors, WMH and MTA are shown in Table 2. Both – DWMH and PVH – were associated only very weakly with vascular risk factors. Without correction for multiple testing, DWMH and PVH were both associated with MTA and focal vascular lesions on MRI.

Ordinal regressions are shown in Table 3. Concerning DWMH, 9 out of 532 patients were deleted due to missing observations (artifacts in MRI in 1, missing vascular risk factor in 8 subjects). As the probability of being in a higher category is modeled, the values of DWMH are placed in descending order. The $R2=0.03$ is very small. A stepwise ordinal regression enters the categorical variable of ''taking antihypertensives'' ($p=0.043$) and the rating of MTA ($p=0.0011$). Because the third group of MTA has only

Table 2. *Associations between deep WMH (DWMH) and periventricular hyperintensities (PVH), MRI parameters, and vascular risk factors (non-parametric correlations (Spearman's ρ, p-values) in case of quantitative variables; Mann–Whitney U-tests (Z, p-value) concerning dichotomised variables labelled with**

Risk factor	DWMH		PVH	
	ρ, Z	p-Value	ρ, Z	p-Value
Gender*	−1.740	0.082	−0.445	0.657
Body Mass Index	0.037	0.395	0.060	0.167
HbA1c	0.016	0.712	0.054	0.217
LDL-cholesterol	−0.044	0.311	−0.058	0.185
HDL-cholesterol	0.033	0.455	−0.017	0.700
Triglyzcerides	0.073	0.095	0.077	0.075
Fibrinogen	−0.023	0.606	−0.035	0.430
Homocysteine	0.070	0.109	0.054	0.211
C-reactive protein	−0.060	0.172	−0.082	0.059
Lipoprotein-a, Lp(a)	0.049	0.556	0.021	0.801
Blood pressure >135/85*	−1.439	0.150	−0.396	0.692
Diastolic BP	0.061	0.162	0.007	0.879
Systolic BP	0.027	0.537	0.000	0.994
Orthostatic hypotension	0.016	0.714	−0.025	0.565
Smoking history*	−0.060	0.952	−0.127	0.899
Antihypertensives*	−1.581	0.114	−1.254	0.210
Lipid-lowering drugs*	−0.623	0.533	−1.452	0.146
Medial temporal lobe atrophy	0.112	0.010	0.142	0.001
Focal vascular lesions on MRI*	−2.239	0.025	−3.043	0.002

Table 3. *Analyses of maximum likelihood estimates of ordinal regressions on DWMH (a) and PVH (b) with vascular risk factors, focal vascular MRI findings, and MTA as predictors*

Parameter	DF	Estimate	Standard error	Wald χ^2	$Pr > \chi^2$
a) Dependent variable DWMH					
Intercept 3	1	−2.4276	0.1868	168.9785	<0.0001
Intercept 2	1	−1.0536	0.1503	49.1066	<0.0001
Intercept 1	1	0.4976	0.1442	11.9040	0.0006
On antihypertensives	1	0.3357	0.1659	4.0940	0.0430
MTA moderate–severe	1	1.4791	0.4096	13.0387	0.0003
MTA mild	1	0.2558	0.2248	1.2944	0.2552
b) Dependent variable PVH					
Intercept 3	1	−2.2943	0.1688	184.8100	<0.0001
Intercept 2	1	−1.9835	0.1552	163.3083	<0.0001
Intercept 1	1	−0.2883	0.1192	5.8500	0.0156
C-reactive protein	1	−0.0324	0.0146	4.9012	0.0268
MTA moderate–severe	1	1.3614	0.4169	10.6668	0.0011
MTA mild	1	0.4274	0.2347	3.3168	0.0686
Focal MRI lesions	1	0.6272	0.2143	8.5652	0.0034

one observation, it is united with group 2. The odds of subjects on antihypertensives being in a higher category of DMWH is 1.4 (95%-CI: 1.01–1.94) times the odds of subjects not taking antihypertensives. That means, people on antihypertensive drugs have a higher risk of DWMH. Comparing patients with mild-MTA versus no-MTA, the odds of being in a higher category of DMWH is 1.3 (95%-CI: 0.83–2.01), comparing moderate–severe MTA versus no-MTA, the odds increase to 4.4 (95%-CI: 1.97–9.80), showing that patients with a higher degree of atrophy of medial temporal structures often have more severe DWMH.

Concerning PVH, 11 out of 532 patients were deleted due to missing observations (vascular risk factor). Again the probability of being in a higher category of PVH was modeled and resulted in a low $R2 = 0.05$. A stepwise ordinal regression enters the categorical variables of MTA ($p = 0.0016$) and focal lesions on MRI ($p = 0.0034$) and the blood parameter C-reactive protein ($p = 0.0016$). People with higher degree of MTA, with focal vascular lesions on MRI, and with lower C-reactive protein level had more PVH. People with focal vascular lesions on MRI were likely to be in a higher category of PVH (1.9; 95%-CI: 1.23–2.85).

Comparing patients with mild-MTA versus no-MTA, the odds of being in a higher category of PVH was 1.5 (95%-CI: 0.97–2.43), comparing moderate–severe MTA versus no-MTA, the odds increased to 3.9 (95%-CI: 1.72–8.83), showing that patients with a higher MTA often have higher PVH. The variable C-reactive protein had a negative estimate. That means, that a high C-reactive protein indicates a low rating of PVH. If C-reactive protein increased by one unit, the odds of being in a higher rather than a lower category of PVH was 0.97 (95%-CI: 0.941–0.996).

Discussion

We found associations between WMH and vascular factors in the community-based age-cohort of the VITA study. Arterial hypertension treated with antihypertensive drugs significantly favored DWMH, and PVH were more frequently found in subjects with focal vascular lesions on MRI. A higher rate of WMH in stroke patients had already been described in many individuals of a rather young age and although in older stroke patients (Inzitari et al., 1987; Schmidt et al., 1992; Breteler et al., 1994a, b; Ylikoski et al., 1995; Henon et al., 1996; Longstreth et al., 1996; Streifler et al., 2003). The importance of arterial hypertension and sBP, especially, for WMH had been established in various samples (Inzitari et al., 1987; Lindgren et al., 1994; Fukuda and Kitani, 1995; Jorgensen et al., 1995; Liao et al., 1996; Longstreth et al., 1996; Coskun et al., 2003; Dijk et al., 2004a; Heijer et al., 2005) and only some had failed to find this relation (Schmidt et al., 1992; Ylikoski et al., 1995; Henon et al., 1996) at least in older subjects (Breteler et al., 1994b). In some studies the successful treatment of hypertension had resulted in less

WMH in patients with controlled hypertension (Fukuda and Kitani, 1995; Liao et al., 1996; Dijk et al., 2004a).

In addition to this relation between arterial hypertension, focal vascular lesions and WMH we found significant associations between both – DWMH and PVH – and focal atrophy of medial temporal lobe structures. Although hippocampal volume loss is not a specific feature of AD, both, the entorhinal cortex and hippocampus have been shown to be less affected by subcortical ischemic vascular dementia than by AD (Du et al., 2002). Thus, our findings might be interpreted in such a way that a degenerative process leading to MTA, as observed in AD, might have favored the occurrence of WMH. The effect was small but significant over the whole spectrum of severity of white matter lesions and severity of MTA. However, in our cross-sectional investigation it was impossible to determine whether MTA was a cause or rather a consequence of WMH (Leeuw et al., 2004; Heijer et al., 2005). The longitudinal part of the VITA will help to elucidate the relation between MTA, AD, vascular risk, and WMH. One clinico-pathological study described vascular changes possibly associated with cerebral amyloid angiopathy in brains of patients with Alzheimer dementia (Janota et al., 1989). That could mean that a vascular factor of degenerative brain disease might favor WMH (Dijk et al., 2004a, b).

Clinico-neuropathological investigations of WMH already indicated that these changes are not of pure vascular-ischemic origin. Studies described vascular changes in some, especially younger patients but also categorized these MRI lesions of the white matter as myelin pallor (Chimowitz et al., 1992), diffuse areas of demyelination (Ferrer et al., 1990), reduced or absent myelin staining, and enlarged perivascular spaces (Van Swieten et al., 1991), loss of myelinated axons (Scheltens et al., 1995a), perivenous damage, and gliosis (Fazekas et al., 1993) or myelin loss, axonal loss, astrogliosis, and dilatation of perivascular space (Ukada et al., 2002). Dilated perivascular spaces were described as associated with brain atrophy (Van Swieten et al., 1991). Clinico-pathological studies also showed scattered microinfarcts or other vascular-type lesions of the white matter in many patients with WMH. Only a few of these autopsied patients belonged to the age group of 75–76 years investigated in the VITA.

Except arterial hypertension, all known classical and novel vascular risk factors were unrelated to DWMH and PVH in the age-cohort of the VITA. Diabetes mellitus, represented by HbA1c levels, did not favor leukoaraiosis. Orthostatic hypotension did not correlate with either type of WMH. Also the lipid status, including total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyzceride and lipoprotein (a) level was not associated with WMH in our birth-cohort. Fibrinogen and homocysteine serum levels were independent from DWMH and PVH. Higher levels of C-reactive protein, discussed as a novel vascular risk factor, were even associated with significantly fewer PVH at age 75. We did not find any relation between smoking or years of smoking and any type of WMH as reported in one stroke sample (Longstreth et al., 1996), but not in others (Jorgensen et al., 1995; Coskun et al., 2003). That diabetes mellitus predicts WMH had been shown in some individuals with strokes at a young age (Schmidt et al., 1992; Ylikoski et al., 1995; Streifler et al., 2003) others did not find an influence of diabetes mellitus on WMH (Henon et al., 1996; Coskun et al., 2003; Schmidt et al., 2004). A relation between cholesterol level and WMH was only described in subjects younger than 75 years (Breteler et al., 1994b). Fibrinogen levels were related to these changes, irrespective of age, in one sample (Breteler et al., 1994b). One population-based study found a significant association between plasma homocysteine levels and both, DWMH and PVH (Vermeer et al., 2002), another one could not replicate this finding (Longstreth et al., 2004).

The weak relation between vascular factors and WMH in the VITA population were not explained by low frequencies of DWMH and PVH. As we investigated an age-cohort at a mean age of 75.6 years with a standard deviation of age of only 0.4 years, our findings could also not be explained by the covariate age. Another explanation might be that we investigated survivors. Patients with vascular risk factors without protective factors might not have survived to the age of 75 or may not be healthy enough to participate in such an epidemiological study. But we could prove that non-participants did not differ from participants with regard to the intake of antihypertensives or antidiabetics.

The weak association between vascular risk factors and WMH together with the high correlation between MTA and these hyperintensities allow us to presume that any pathological process of preclinical Alzheimer dementia might favor the occurrence or severity of both, DWMH and PVH. However, the cross-sectional design of this study does not allow the establishment of a causal relationship. It is possible that brain shrinkage with loss of interconnectivity and consecutive loss of myelin and widening of perivascular spaces explains some variation of WMH in old age. Such an association between brain atrophy and WMH has already been described clinically (Ylikoski et al., 1995; Henon et al., 1996; Capizzano et al., 2004; Leeuw et al., 2004) and neuropathologically (Van Swieten et al., 1991).

A strong relation between brain atrophy and white matter changes may be valid for the very elderly investigated in

this study but may not necessarily apply to younger patients, i.e., with Binswanger's disease following malignant arterial hypertension. At a younger age, leukoencephalopathy and focal subcortical lesions may even coexist with a determined genetic origin called CADASIL. Moreover, infarcts were significantly associated with the ratings of hyperintensities in our study as also described by others (Inzitari et al., 1987; Breteler et al., 1994b; Fukuda and Kitani, 1995; Ylikoski et al., 1995; Longstreth et al., 1996; Coskun et al., 2003). We, thus, do not claim that WMH are mainly caused by brain shrinkage at every age group. Moreover, we think it possible that WMH in the very elderly are causally related not only to vascular factors, e.g. hypertension, but also to cerebral atrophy and degenerative brain disease, such as AD.

Acknowledgement

This work was supported by the Ludwig Boltzmann Society and carried out at the Ludwig Boltzmann Institute of Aging Research.

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