Structural brain changes in migraine and cluster headache

Arkink, E.B.

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Infratentorial hyperintensities and associated risk of mortality in an elderly cohort

E.B. Arkink
G.M. Terwindt
G.J. Blauw
J. van der Grond
M.A. van Buchem
M.D. Ferrari
M.C. Kruit
on behalf of the PROSPER Study Group

Submitted

Abstract

Objective:

To assess associations of infratentorial hyperintensities (IHs) with cardiovascular risk factors, migraine, and other lesion types and to investigate whether their presence is predictive of mortality.

Methods:

We examined the prevalence and severity of IHs in 545 participants of the MRI substudy of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). After study completion, mortality of study participants was followed-up. Logistic regression models assessed associations between IHs, cardiovascular risk factors, migraine, and other neuroimaging characteristics. Cox proportional hazard models evaluated overall mortality risk associated with IHs.

Results:

Higher age, smoking, and lower body mass indices correlated with the presence and severity of IHs. Overall, migraine did not increase the risk of IHs. However, male migraineurs had more severe IHs (odds ratio (OR) 2.50, 95% confidence interval (95%CI) 1.01-6.15) than male controls. IHs correlated with the presence of lacunar (OR 2.02, 95%CI 1.34-3.07) and infratentorial OR 2.04, 95%CI 1.23-3.40) infarcts, supratentorial white matter hyperintensity load (OR 3.61, 95%CI 2.31-5.65) and enlarged Virchow-Robin spaces. Participants with severe, confluent IHs had an increased risk of death (hazard ratio 1.85, 95%CI 1.21-2.88) compared to those without IHs.

Conclusions:

Higher age, smoking, lower body mass indices and -in males only- migraine predispose for IHs. The co-occurrence of IHs with other ischemic markers of small vessel disease suggests that IHs share common pathophysiological pathways. Higher mortality among participants with IHs makes their identification on MRI potentially clinically relevant.

Introduction

On T2-weighted brain magnetic resonance imaging (MRI) scans, infratentorial hyperintensities (IHs) are focal or diffuse lesions in the cerebellar white matter, cerebellar peduncles, and brainstem, mostly located in the pons.[1] IHs are relatively unknown, underrecognized and only scarcely investigated. This is in great contrast with supratentorial white matter hyperintensities (WMHs), that are strongly associated with aging and chronic conditions, such as hypertension and diabetes, leading to white matter injury through microvascular, inflammatory, and metabolic mechanisms.[2-5]

IHs were present in 23-48% of patients with clinical manifestations of atherosclerosis, vascular dementia and stroke.[6-8] In these cases, IHs correlated with age and the presence of supratentorial leukoaraiosis, atrophy and lacunar cerebral infarcts,[7;8] suggesting that IHs are also due to small vessel disease.[7;9] In a population-based study we reported that migraine was associated with higher prevalence and higher rate of progression of IHs, independent from age, sex and cardiovascular determinants.[1]

It is unknown whether in elderly people migraine is still associated with an increased prevalence of IHs. More in general, to our knowledge, data on prevalence and associations of IHs in the elderly general population are largely lacking. Although pontine hyperintensities were associated with poor clinical outcome after supratentorial ischemic stroke,[8] it is unknown if IHs are predictive of mortality in the general elderly population.

We evaluated the presence, severity, and associated neuroimaging characteristics of IHs in an elderly population with or at risk of vascular disease. We determined which risk factors correlated with IHs, with a particular interest for migraine. Further, we investigated the prognostic value of IHs regarding overall mortality.

Methods

Study population

Participants were included from the MRI substudy of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), a placebo-controlled trial studying risk reduction by pravastatin of cardiovascular and cerebrovascular disease in elderly participants at risk.[10]

Follow-up MRI scans were available in 545 of 646 participants included at baseline (aged 73-85 years at follow-up); the remaining participants were incapable of undergoing MRI scans due to illness or death, MRI contraindications, technical issues, loss to follow-up or informed consent withdrawal. For subanalyses in migraineurs, in 535/545 participants lifetime migraine status was evaluated using a previously used and validated questionnaire[11] and checked by migraine experts (G.M.T., M.C.K.), addressing International Headache Society criteria.[12] Validation of this questionnaire in a separate elderly cohort of 20 migraineurs and 6 headache-free controls resulted in 95% sensitivity and 100% specificity.

Mortality of study participants was continuously followed-up after study completion. The cut-off date for determining mortality was February 10, 2014, which was up to 12.9 years after follow-up MRI.

Standard protocol approvals, registrations, and patient consents

The institutional review board approved the study. All participants gave written informed consent. All consenting participants were enrolled from May 2, 1998 onwards.

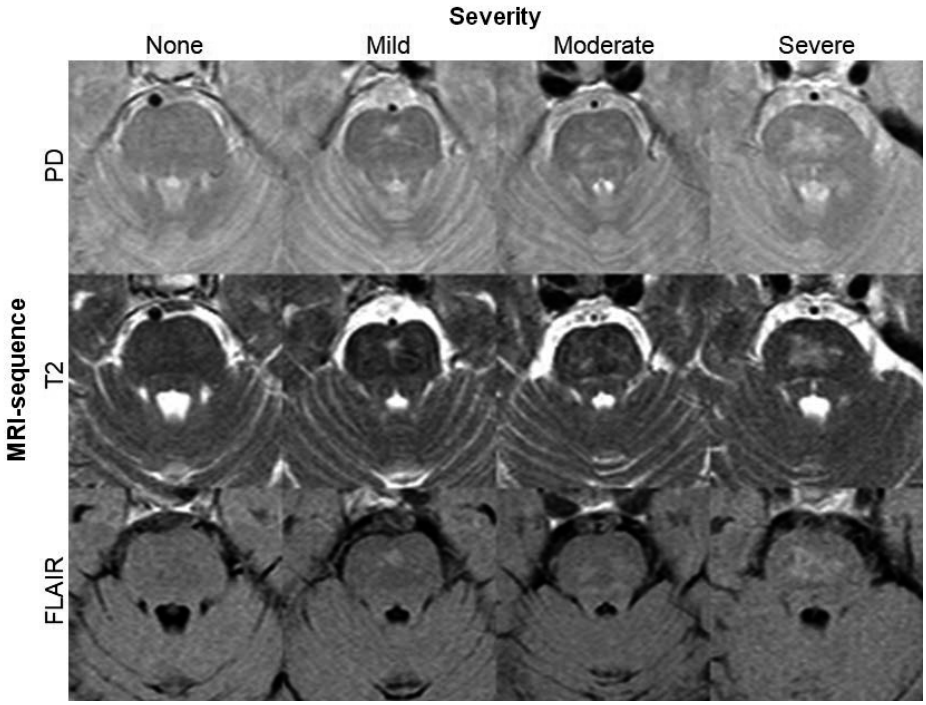
MRI acquisition and scoring of neuroimaging characteristics

T2-weighted, proton density-weighted, fluid-attenuated inversion recovery (FLAIR), and T2*-weighted images were acquired at a 1.5 T MRI system (NT-ACS, Philips, Best, the Netherlands). One rater (E.B.A.), blinded for clinical information, scored IHs. These were defined as non-lacunar hyperintense lesions on T2-weighted and proton density-weighted images. We further differentiated between pontine and cerebellar hyperintensities, and we graded severity of IHs

(0=none, 1=mild (single punctate), 2=moderate (multiple punctate, beginning confluent), 3=severe (large confluent)), similar to the Fazekas scale for deep white matter lesions (see Figure 8.1).[13]

Cerebral infarcts (supracortical (cortical, lacunar), infratentorial),[14;15] cerebral microbleeds (lobar, basal ganglia, infratentorial)[16] and enlarged Virchow-Robin spaces (VRS) (semioval center, basal ganglia, subinsular, mesencephalon)[17] were scored using previously established criteria. VRS were differentiated from lacunar infarcts based on size, location, (longitudinal) shape and the absence of a surrounding high signal intensity rim on FLAIR images. Pontine and cerebellar parenchymal defects isointense to CSF on all sequences were differentiated from IHs and VRS and classified as infratentorial infarcts. Due to incomplete acquisition and MRI artifacts, microbleed detection was not feasible in 20/545 participants.

Figure 1 Examples of IHs Proton density-weighted (PD, upper row), T2-weighted (middle row) and FLAIR (bottom row) MR images at the midpontine level showing examples of no (1st column), mild (2nd column), moderate (3rd column) and severe (4th column) IHs



Supratentorial WMHs were segmented automatically as hyperintensities in T2-weighted, proton density-weighted and FLAIR images using Software for Neuro-Image Processing in Experimental Research (SNIPER).[18] WMH volumes above the 80th percentile were classified as high WMH-load.[19] Intracranial and brain parenchyma volume were also calculated with SNIPER. Atrophy was calculated using the formula: atrophy (%)=([intracranial volume-brain parenchyma volume]/[intracranial volume])x100%.

Statistics

We calculated the predictive value of established cardiovascular risk factors for the presence and severity of IHs using univariate binary and ordinal logistic regression analyses, respectively (SPSS 20.0.0, Chicago, IL, USA). Then, multivariate binary and ordinal logistic regression analyses were performed taking into account all these cardiovascular determinants in one model. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to identify effect direction of each determinant. P-values <0.05 were considered significant. To study the effect of migraine, these initial analyses were repeated for a subgroup with all controls and definite migraineurs, including migraine as an additional cardiovascular risk factor. Additional explorative analyses were performed differentiating between migraine with and without aura. Based on previous reports of sex differences in the relationship between migraine and cerebrovascular damage,[20] we also a priori stratified between male and female migraineurs.

The association between IHs and other types of cerebrovascular damage was assessed using univariate binary (prevalence) and ordinal (severity) logistic regression analyses.

We calculated Kaplan-Meier survival curves for overall mortality for no, mild, moderate and severe IHs. Cox proportional hazard models were applied to estimate the risk of overall mortality associated with IHs, adjusting for age, sex, body mass index and current smoking (model 1), additional cardiovascular determinants (systolic and diastolic blood pressure, cholesterol and triglyceride levels, alcohol consumption, and history of hypertension/diabetes/myocardial infarction/stroke or transient ischemic attack; model 2) and, in addition to model 2, other types of neuroimaging characteristics (presence of any cerebral infarcts, microbleeds and/or high WMH-load; model 3). Hazard ratios (HRs) with 95% CIs were calculated.

Results

The prevalence of IHs was 42% (40% pontine, 6% cerebellar; n=235). These IHs were mild in n=73 (13%), moderate in n=123 (23%), and severe in n=39 (7%). Main predictors for prevalence and severity of IHs were higher age, smoking, and lower body mass index (Table 8.1).

Lifetime migraine was diagnosed in 66/535 participants (12%; men 6%, women 19%). Of these, 26 had migraine with aura, 37 migraine without aura, and in 3 participants aura status was uncertain. In total 371 participants served as controls. In the remaining 98 participants, data was missing, other types of headache were diagnosed or severe headache history did not fully meet migraine criteria ('probable/possible migraine'). Comparison of the demographics showed that migraineurs were more often female (70% versus 36%; p<0.001; reflecting the normal sex distribution of migraine), had more often hypertension (82% versus 59%; p<0.001) and consumed less alcohol (5.03±6.50 versus 7.78±8.97; p=0.016) than controls (Table 8.2). Further, migraineurs without aura were less likely to smoke (8% vs 23%; p=0.036) while migraineurs with aura had higher total cholesterol levels (6.07±0.76 vs 5.71±0.84; p=0.039), compared to controls.

Lifetime migraine was not an independent predisposing factor compared to controls, neither for prevalence (47% in migraine vs 42% in controls) nor for severity of IHs (Table 8.3). Prevalence and severity of IHs did not differ in subgroups of migraine with and without aura compared to controls either. Male migraineurs however had more frequent (65% vs 39%, univariate analysis) and more severe IHs (univariate and multivariate analysis) than male controls. Migraine was not an independent predictor of IHs in females.

The presence of cerebral infarcts was associated with a higher presence (43% vs 27%) and severity (p<0.001) of IHs. IHs were particularly associated with lacunar and infratentorial infarcts, but not with cortical infarcts (Table 8.4). High WMH-load was associated with a higher presence (31% vs 11%) and severity (p<0.001) of IHs as well. Higher VRS scores in any location also strongly correlated with higher prevalence and severity of IHs. Microbleeds and atrophy were not associated with IHs in this cohort.

Table 8.1 Comparison of cardiovascular risk factors for prevalence and severity of IHs

	All participants	IHs prevalence		IHs severity			Prevalence (logistic regression)		Severity (ordinal regression)	
	n=545	None n=310	Any n=235	Mild n=73	Moderate n=123	Severe n=39	Univariate	Multivariate	Univariate	Multivariate
Age (years)	77.2±3.2	76.9±3.1	77.7±3.2	77.9±3.3	77.5±3.2	78.3±3.2	1.08 [1.03-1.14]*	1.09 [1.03-1.16]*	1.08 [1.03-1.14]*	1.08 [1.02-1.14]*
Female sex	236 (43)	128 (42)	108 (46)	29 (40)	56 (46)	23 (59)	1.19 [0.84-1.67]	1.22 [0.80-1.85]	1.26 [0.91-1.74]	1.33 [0.90-1.97]
Current smoker	114 (21)	55 (18)	59 (25)	15 (21)	34 (28)	10 (26)	1.55 [1.03-2.35]*	1.83 [1.09-3.06]*	1.57 [1.06-2.31]*	2.02 [1.25-3.27]*
Hypertension	344 (63)	199 (64)	145 (62)	38 (52)	81 (66)	26 (67)	0.90 [0.63-1.28]	1.23 [0.77-1.95]	0.99 [0.71-1.39]	1.43 [0.92-2.23]
Diabetes	91 (17)	57 (18)	34 (14)	12 (16)	14 (11)	8 (21)	0.75 [0.47-1.19]	0.92 [0.55-1.54]	0.77 [0.49-1.21]	0.93 [0.57-1.51]
Myocardial infarction	67 (12)	41 (13)	26 (11)	7 (10)	17 (14)	2 (5)	0.82 [0.48-1.38]	0.89 [0.47-1.71]	0.81 [0.49-1.35]	0.98 [0.52-1.82]
Stroke/TIA	87 (16)	49 (16)	38 (16)	11 (15)	20 (16)	7 (18)	1.03 [0.65-1.63]	0.81 [0.45-1.47]	1.05 [0.68-1.64]	0.89 [0.51-1.57]
Vascular disease	234 (43)	132 (43)	102 (43)	34 (47)	55 (45)	13 (33)	1.03 [0.73-1.46]	1.22 [0.73-2.02]	0.98 [0.70-1.35]	1.13 [0.70-1.82]
Systolic blood pressure (mmHg)	157.5 ±21.8	158.5 ±21.4	156.1 ±22.2	156.3 ±22.1	155.2 ±20.1	158.9 ±28.3	0.99 [0.99-1.00]	0.99 [0.98-1.01]	1.00 [0.99-1.00]	1.00 [0.99-1.01]
Diastolic blood pressure (mmHg)	85.9±11.0	86.4±11.0	85.2±11.1	84.9±10.7	85.6±11.0	84.6±12.3	0.99 [0.98-1.01]	1.00 [0.98-1.02]	0.99 [0.98-1.01]	1.00 [0.98-1.02]
Body mass index (kg/m^2)	26.7±3.6	27.1±3.6	26.1±3.5	26.1±3.4	26.2±3.5	25.4±3.8	0.92 [0.88-0.97]*	0.93 [0.88-0.98]*	0.92 [0.88-0.97]*	0.93 [0.88-0.98]*
Total cholesterol (mmol/l)	5.8±0.9	5.8±0.9	5.7±0.8	5.8±0.8	5.8± 0.9	5.6±0.8	0.97 [0.80-1.19]	0.94 [0.75-1.18]	0.95 [0.78-1.14]	0.89 [0.72-1.11]
Triglyceride (mmol/l)	1.5±0.7	1.5±0.7	1.4±0.6	1.6±0.7	1.4±0.6	1.4±0.6	0.83 [0.64-1.07]	0.90 [0.67-1.19]	0.79 [0.62-1.02]	0.87 [0.66-1.15]
Alcohol (units/week last month)	6.7±8.3	7.1±8.4	6.3±8.2	7.2±9.2	6.2±8.2	5.0±5.4	0.99 [0.97-1.01]	0.99 [0.97-1.02]	0.90 [0.78-1.03]	0.99 [0.97-1.01]

Mean±SD; number (%); *p<0.05

Table 8.2 Demographics for migraine patients and headache-free controls

	All n=545	Controls n=371	Migraine		
			Total n=66	MA n=26	MO n=37
Age (years)	77.3± 3.2	77.0±3.2	77.8±3.1	77.9±3.2	77.8±3.2
Female sex	236 (43)	134 (36)	46 (70)†	19 (73)†	25 (68)†
Current smoker	114 (21)	85 (23)	8 (12)	4 (15)	3 (8)*
Hypertension	344 (63)	219 (59)	54 (82)†	19 (73)	34 (92)†
Diabetes	91 (17)	57 (15)	8 (12)	3 (12)	5 (14)
Myocardial infarction	67 (12)	50 (13)	7 (11)	3 (12)	4 (11)
Stroke/TIA	87 (16)	58 (16)	11 (17)	3 (12)	8 (22)
Vascular disease	234 (43)	168 (45)	26 (39)	10 (38)	15 (41)
Blood pressure:					
systolic (mmHg)	157.5±21.8	157.2±21.3	156.5±21.4	156.8±17.5	158.2±23.7
diastolic (mmHg)	85.9±11.0	85.3±10.7	87.1±12.5	85.2±10.6	89.4±13.5
Body mass index (kg/m^2)	26.7±3.6	26.7±3.8	26.5±3.8	27.1±4.0	26.4±3.7
Total cholesterol (mmol/l)	5.8±0.9	5.7±0.8	5.9±0.9	6.1±0.8*	5.7±0.9
Triglycerides (mmol/l)	1.5±0.7	1.5±0.7	1.5±0.6	1.6±0.6	1.4±0.7
Alcohol (units/week last month)	6.7±8.3	7.8±9.0	5.0±6.5*	5.5±7.8	4.7±5.5

Mean±SD, number (%); TIA=transient ischemic attack; MA=migraine with aura; MO=migraine without aura; Independent samples T-test for continuous (except for alcohol consumption; Mann-Whitney U test used), Fisher's exact test for categorical variables and comparing migraine or migraine subgroups to controls; *p<0.05, †p<0.001. Figures of migraine subgroups do not sum up to total due to uncertainty about subclassification in some migraineurs.

The mean follow-up duration for determining mortality was 9.2(±3.7) years after follow-up MRI scan. In this period, 348 of 545 participants (64%; 170 with IHs) had deceased. Figure 8.2 shows the corresponding Kaplan-Meier survival curve for these participants. The presence of any IH independently increased the risk of mortality after correction for age, sex, body mass index and smoking, additional cardiovascular risk factors, and other neuroimaging characteristics (HR 1.32, 95% CI 1.03-1.64). Those participants with severe (large, confluent) IHs were at highest risk (HR 1.87, 95% CI 1.21-2.88; model 3) (Table 8.4). When comparing migraineurs and controls, similar survival curves were found for the association between infratentorial hyperintensities and mortality (no significant differences between groups).

Table 8.3 Associations between IHs and other neuroimaging characteristics

	IHs prevalence		IHs severity			Prevalence (binary logistic regression)	Severity (ordinal logistic regression)
	None n=310	Any n=235	Mild n=73	Moderate n=123	Severe n=39		
Infarcts	84 (27)	100 (43)	25 (34)	56 (46)	19 (49)	1.98 [1.38-2.84]†	2.04 [1.44-2.86]†
Cortical	35 (11)	31 (13)	9 (12)	15 (12)	7 (18)	1.19 [0.71-1.99]	1.23 [0.76-2.01]
Lacunar	50 (11)	66 (28)	15 (21)	37 (30)	14 (36)	2.02 [1.34-3.07]†	2.12 [1.44-3.12]†
Infratentorial	29 (9)	41 (17)	9 (12)	22 (18)	10 (26)	2.04 [1.23-3.40]*	2.18 [1.37-3.48]*
Microbleeds	66 (22)	61 (27)	18 (26)	33 (28)	10 (28)	1.33 [0.89-1.99]	1.31 [0.89-1.93]
Lobar	53 (18)	51 (23)	13 (19)	30 (25)	8 (22)	1.38 [0.90-2.12]	1.40 [0.93-2.10]
Basal ganglia	14 (5)	10 (4)	2 (3)	6 (5)	2 (6)	0.92 [0.42-2.20]	1.05 [0.47-2.30]
Infratentorial	16 (5)	12 (5)	4 (6)	3 (3)	5 (14)	1.01 [0.47-2.18]	1.14 [0.55-2.36]
VRS: semioval center							
None	165 (53)	101 (43)	33 (45)	50 (41)	18 (46)	reference	reference
<5 on either side	81 (26)	72 (31)	21 (29)	40 (33)	11 (28)	1.45 [0.97-2.17]	1.42 [0.97-2.09]
=>5 on either side	64 (21)	62 (26)	19 (26)	33 (27)	10 (26)	1.58 [1.03-2.43]*	1.53 [1.02-2.30]*
VRS: basal ganglia							
Substantia innominata only, <5 on either side	46 (15)	14 (6)	4 (5)	8 (7)	2 (5)	reference	reference
Substantia innominata only, =>5 on either side	33 (11)	10 (4)	3 (4)	5 (4)	2 (5)	1.00 [0.39-2.52]	1.00 [0.40-2.49]
Lentiform nucleus, <5 on either side	77 (25)	41 (17)	17 (23)	20 (16)	4 (10)	1.75 [0.86-3.55]	1.63 [0.82-3.27]
Lentiform nucleus, 5-9 on either side or <5 in the caudate nucleus	63 (20)	44 (19)	18 (25)	20 (16)	6 (15)	2.30 [1.13-4.67]*	2.13 [1.06-4.26]*
Lentiform nucleus, =>10 on either side and <5 in the caudate nucleus	63 (20)	73 (31)	23 (32)	39 (32)	11 (28)	3.81 [1.92-7.57]†	3.54 [1.82-6.90]†
Lentiform nucleus, =>10 on either side and =>5 in the caudate nucleus	28 (9)	53 (23)	8 (11)	31 (25)	14 (36)	6.22[2.93-13.21] †	6.95 [3.41-14.20] †
VRS: subinsular							
None	76 (25)	44 (19)	15 (21)	24 (20)	5 (13)	reference	reference
<5 on either side	124 (40)	77 (33)	27 (37)	37 (30)	13 (33)	1.07 [0.67-1.72]	1.08 [0.69-1.71]
=>5 on either side	110 (35)	114 (49)	31 (42)	62 (50)	21 (54)	1.79 [1.14-2.82]*	1.83 [1.18-2.84]*
VRS: mesencephalon	131 (42)	131 (56)	41 (56)	66 (54)	24 (62)	1.72 [1.22-2.42]*	1.67 [1.20-2.32]*
High WMH-load	35 (11)	74 (31)	15 (21)	38 (31)	21 (54)	3.61 [2.31-5.65]†	3.97 [2.66-5.92]†
Atrophy (%)	27.35 ±3.04	27.10 ±3.78	27.60 ±3.99	26.85± 3.43	27.39 ±3.91	0.99 [0.94-1.04]	1.01 [0.97-1.06]

Mean±SD; number (%); *p<0.05, †p<0.001; VRS=Virchow Robin spaces; WMH=white matter hyperintensity

Discussion

The most surprising finding of this study is that IHs are associated with higher mortality, independent of cardiovascular risk factors and other types of cerebrovascular damage. We identified increasing age, smoking and low body mass index as the main predictors of IHs. Where previously migraine was identified as a risk factor for progressive IHs in younger participants irrespective of sex, in this elderly cohort migraine only increased the risk of IHs in male participants. IHs strongly correlated with the presence of high supratentorial WMH-load, lacunar and infratentorial infarcts, and VRS, which suggests that IHs are another hallmark of small vessel disease.

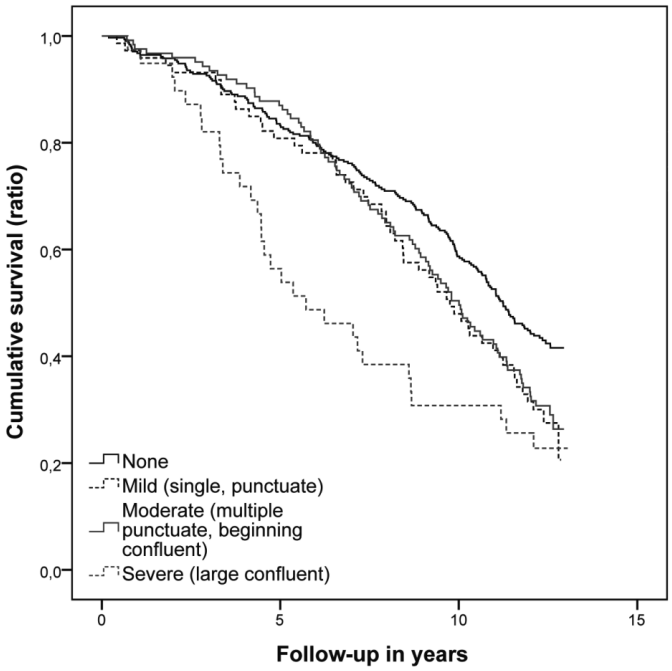
A major strength of this study is that we studied a considerably large population-based study sample to examine IHs and their associations with cardiovascular risk factors and other types of cerebrovascular damage.[7;8] We could confirm age as a risk factor[7] and we could add smoking and lower body mass index as predisposing factors. Although a lower body mass index has also been reported as a predisposing factor for subclinical cerebral infarction[21-23] and supratentorial WMH-load,[24] this finding seems counterintuitive. An explanation for this increased risk of subclinical cerebrovascular damage may be the "obesity paradox": a lower body mass index might indicate malnutrition, for instance due to (chronic) medical or psychogeriatric conditions or drug abuse. Furthermore, more obese participants in our population may have received more aggressive medical treatment in the past as they were recognized at increased risk of vascular disease.[25]

Table 8.4 Risk of mortality associated with presence and severity of IHs

		Model 1		Model 2		Model 3
	d/n	HR (95% CI)	d/n	HR (95% CI)	d/n	HR (95% CI)
No IHs	178/310	1.00 (reference)	178/310	1.00 (reference)	173/301	1.00 (reference)
Any IH	170/235	1.36 [1.10-1.68]*	170/235	1.46 [1.17-1.82]†	162/224	1.32 [1.05-1.64]*
Mild IHs	53/73	1.32 [0.97-1.80]	53/73	1.37 [1.00-1.88]*	50/69	1.33 [0.97-1.81]
Moderate IHs	87/123	1.27 [0.98-1.64]	87/123	1.38 [1.06-1.80]*	84/119	1.22 [0.93-1.60]
Severe IHs	30/39	1.90 [1.28-2.82]*	30/39	2.17 [1.44-3.26]†	28/36	1.85 [1.21-2.88]*

d/n=deceased/total number of participants; HR=hazard ratio; CI=confidence interval; corrected for age, sex, smoking and body mass index (model 1), other cardiovascular risk factors (model 2) and other types of cerebral damage (model 3); *p<0.05, †p<0.001.

Figure 8.2 Kaplan-Meier survival curve in relation to IH severity; depicted are participants with no (black solid line), mild (black dotted line), moderate (grey solid line) and severe (grey dotted line) IHs



Similarly, participants in our study may also have been treated adequately for other traditional risk factors that strongly correlate with supratentorial WMH-load, such as hypertension and diabetes. This might explain why we did not find an association of these determinants with IHs. Hence, the increased risk of vascular disease also represents a limitation of our study and results might therefore not be generalizable to the entire population.

Previously, IHs were associated with the presence of supratentorial leukoaraiosis, supratentorial atrophy and lacunar cerebral infarcts.[7;8] Therefore, it has been proposed that they are also the consequence of small vessel disease.[7;9] The high prevalence of IHs in small vessel diseases like CADASIL (in up to 100% in those older than 50 years of age) supports this notion.[26] Hypoperfusion in border zones between different vascular territories in the pontine and cerebellar areas has been suggested to contribute to this process.[7;27;28] In the current study, we found strong correlations of IHs with high supratentorial WMH-load, lacunar and infratentorial infarcts, that

all can be considered ischemic markers of cerebral small vessel disease.[29] Despite these associated neuroimaging characteristics, we were unable to associate IHs to cerebral microbleeds, a hemorrhagic marker of microangiopathy, possibly because our study lacked sufficient power. However, it has also been suggested that distinct inflammatory pathways may underlie ischemic and hemorrhagic cerebrovascular MRI markers in small vessel disease.[29] Thus, an alternative explanation for a weaker association between IHs and microbleeds might be that they are the result of different inflammatory cascades causing endothelial cell dysfunction and damage. Future research should clarify whether the inflammatory pathways associated with ischemic lesions in small vessel disease can be related to IHs as well.

In spite of the high prevalence of other cardiovascular risk factors in our elderly population, the more unfavorable cardiovascular risk profiles in migraineurs, and the relatively small number of migraine cases, lifetime migraine still independently increased the severity of IHs in males. Together with the higher risk of subclinical cerebellar infarcts[19] and infratentorial microbleeds,[30] these data again suggest that migraine modifies the risk of infratentorial cerebrovascular damage. Due to recall bias and by using strict migraine criteria we likely underdiagnosed the prevalence of migraine compared to literature.[11] The consequential small number of migraine cases disallowed us to assess effects of attack frequency, activity, duration, and chronicity of migraine, which is another limitation of our study. Anyhow, our findings again suggest that migraine should be added to the known risk factors for cerebrovascular small vessel disease. Moreover, it suggests that migraine should not be disregarded as a risk factor for cerebrovascular damage in elderly male participants. In previous studies, particularly women, and not men, with migraine were at increased risk of subclinical brain lesions.[20] Moreover, female migraineurs are at higher risk of ischemic stroke compared to male patients.[31] The reason for this discrepancy is unclear. Previous population-based studies may have been underpowered to measure effects in men, whereas our study may have lacked sufficient power to detect differences in female migraineurs. Moreover, other cardiovascular risk factors might have obscured the role of migraine in our female population, as the association between migraine and cardiovascular risk is especially increased in young women.[32]

The association between infratentorial hyperintensities and mortality makes their identification on MRI potentially clinically relevant. Unfortunately, the individual causes of death were not available for all deceased participants at the chosen study end point and thus, we were not able to differentiate between overall, cardiovascular and stroke-related mortality like in previous observations in this cohort.[33] Therefore we could not verify whether the increased mortality in participants with infratentorial hyperintensities can be ascribed to cardiovascular and cerebrovascular events, as reasonably might be expected in this cohort of elderly individuals with or at increased risk of vascular disease. Future studies should tackle this issue to identify patients at increased risk of these mortality causes, as they might benefit most from close cardiovascular risk monitoring and preventive medical care.

References

1. Kruit MC, Launer LJ, Ferrari MD, van Buchem MA. Brain stem and cerebellar hyperintense lesions in migraine. Stroke 2006;37:1109-1112.
2. Pantoni L, Garcia JH. Pathogenesis of leukoaraiosis: a review. Stroke 1997;28:652-659.
3. Rosenberg GA, Wallin A, Wardlaw JM et al. Consensus statement for diagnosis of subcortical small vessel disease. J Cereb Blood Flow Metab 2016;36:6-25.
4. Tamura Y, Araki A. Diabetes mellitus and white matter hyperintensity. Geriatr Gerontol Int 2015;15 Suppl 1:34-42.
5. Cloonan L, Fitzpatrick KM, Kanakis AS, Furie KL, Rosand J, Rost NS. Metabolic determinants of white matter hyperintensity burden in patients with ischemic stroke. Atherosclerosis 2015;240:149-153.
6. Bastos Leite AJ, van der Flier WM, van Straaten EC, Scheltens P, Barkhof F. Infratentorial abnormalities in vascular dementia. Stroke 2006;37:105-110.
7. Kwa VI, Stam J, Blok LM, Verbeeten B, Jr. T2-weighted hyperintense MRI lesions in the pons in patients with atherosclerosis. Amsterdam Vascular Medicine Group. Stroke 1997;28:1357-1360.
8. Mantyla R, Pohjasvaara T, Vataja R et al. MRI pontine hyperintensity after supratentorial ischemic stroke relates to poor clinical outcome. Stroke 2000;31:695-700.
9. Erbay SH, Brewer E, French R et al. T2 hyperintensity of medial lemniscus is an indicator of small-vessel disease. AJR Am J Roentgenol 2012;199:163-168.
10. Shepherd J, Blauw GJ, Murphy MB et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002;360:1623-1630.
11. Launer LJ, Terwindt GM, Ferrari MD. The prevalence and characteristics of migraine in a population-based cohort: the GEM study. Neurology 1999;53:537-542.
12. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013;33:629-808.
13. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. AJR Am J Roentgenol 1987;149:351-356.
14. Bokura H, Kobayashi S, Yamaguchi S. Distinguishing silent lacunar infarction from enlarged Virchow-Robin spaces: a magnetic resonance imaging and pathological study. J Neurol 1998;245:116-122.

15. Price TR, Psaty B, O'Leary D, Burke G, Gardin J. Assessment of cerebrovascular disease in the Cardiovascular Health Study. Ann Epidemiol 1993;3:504-507.
16. Greenberg SM, Vernooij MW, Cordonnier C et al. Cerebral microbleeds: a guide to detection and interpretation. Lancet Neurol 2009;8:165-174.
17. Patankar TF, Mitra D, Varma A, Snowden J, Neary D, Jackson A. Dilatation of the Virchow-Robin space is a sensitive indicator of cerebral microvascular disease: study in elderly patients with dementia. AJNR Am J Neuroradiol 2005;26:1512-1520.
18. Admiraal-Behloul F, van den Heuvel DM, Olofsen H et al. Fully automatic segmentation of white matter hyperintensities in MR images of the elderly. Neuroimage 2005;28:607-617.
19. Kruit MC, van Buchem MA, Hofman PA et al. Migraine as a risk factor for subclinical brain lesions. JAMA 2004;291:427-434.
20. Palm-Meinders IH, Koppen H, Terwindt GM et al. Structural brain changes in migraine. JAMA 2012;308:1889-1897.
21. Bouchi R, Babazono T, Yoshida N et al. Silent cerebral infarction is associated with the development and progression of nephropathy in patients with type 2 diabetes. Hypertens Res 2010;33:1000-1003.
22. Kotani K, Osaki Y, Sakane N, Adachi S, Ishimaru Y. Risk factors for silent cerebral infarction in the elderly. Arch Med Res 2004;35:522-524.
23. Seliger SL, Longstreth WT, Jr., Katz R, et al. Cystatin C and subclinical brain infarction. J Am Soc Nephrol 2005;16:3721-3727.
24. Driscoll I, Gaussoin SA, Wassertheil-Smoller S et al. Obesity and Structural Brain Integrity in Older Women: The Women's Health Initiative Magnetic Resonance Imaging Study. J Gerontol A Biol Sci Med Sci 2016.
25. Katsnelson M, Rundek T. Obesity paradox and stroke: noticing the (fat) man behind the curtain. Stroke 2011;42:3331-3332.
26. van den Boom R, Lesnik Oberstein SA, Ferrari MD, Haan J, van Buchem MA. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: MR imaging findings at different ages--3rd-6th decades. Radiology 2003;229:683-690.
27. Tatu L, Moulin T, Bogousslavsky J, Duvernoy H. Arterial territories of human brain: brainstem and cerebellum. Neurology 1996;47:1125-1135.
28. Pullicino P, Ostrow P, Miller L, Snyder W, Munschauer F. Pontine ischemic rarefaction. Ann Neurol 1995;37:460-466.
29. Shoamanesh A, Preis SR, Beiser AS et al. Inflammatory biomarkers, cerebral microbleeds, and small vessel disease: Framingham Heart Study. Neurology 2015;84:825-832.
30. Arkink EB, Terwindt GM, de Craen AJ et al. Infratentorial Microbleeds: Another Sign of Microangiopathy in Migraine. Stroke 2015;46:1987-1989.
31. Schürks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T. Migraine and cardiovascular disease: systematic review and meta-analysis. BMJ 2009;339:b3914.
32. Kurth T, Diener HC. Migraine and stroke: perspectives for stroke physicians. Stroke 2012;43:3421-3426.
33. Altmann-Schneider I, Trompet S, de Craen AJ et al. Cerebral microbleeds are predictive of mortality in the elderly. Stroke 2011;42(3):638-644.