A MRI study into the effect of pravastatin on cerebrovascular pathologies

Dam, V.H. ten

6. Periventricular white matter hyperintensities predict occurrence of subcortical cerebral infarcts

VH ten Dam, DMJ van den Heuvel, AJM de Craen, ELEM Bollen, RGJ Westendorp, GJ Blauw, MA van Buchem

Abstract

Background and purpose The association between white matter hyperintensities (WMH) and silent brain infarcts supports the concept of small-vessel disease underlying these two phenomena. However, various stroke subtypes have different risk profiles, while periventricular and deep WMH also may have a different risk profile. The aim of our study was to explore the longitudinal association of both types of WMH with subtypes of cerebral infarcts in order to learn more about possible, shared pathways.

Methods All data come from the MRI-study, nested within the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). In this MRI-study we performed repeated MRI scans in 554 subjects with an average interval of 33 (SD ± 1.4) months. All participants were aged 70-82 years at baseline. Volume of white matter hyperintensities was assessed with a semi-automated quantification method. Cerebral infarcts were identified on hard copy excluding cerebral bleedings, hemorrhagic infarcts and Virchow-Robin spaces. For this analysis, complete data were available for 533 subjects.

Results Volume of total, periventricular, and deep WMH was strongly associated with subcortical infarcts at baseline (all p-values < 0.001). Moreover, a high volume of total WMH at baseline predicted the occurrence of subcortical infarcts during follow-up (OR 4.6, 95% CI 1.9-10.9). The increased incidence of subcortical infarcts was mainly attributable to the periventricular WMH (OR 4.6, 95% CI 2.0-10.8) and not to the deep WMH (OR 1.7, 95% CI 0.9 – 3.9). There was no cross-sectional or longitudinal association between WMH and cortical infarcts.

Conclusion Our results suggest that periventricular WMH and subcortical brain infarcts are likely to have the same underlying pathophysiology.

Introduction

White matter hyperintensities (WMH) and cerebral infarcts are common findings on magnetic resonance images (MRI) of the aging brain. Both WMH and cerebral infarcts are likely to be manifestations of cerebrovascular disease [1-4]. Depending on its anatomical localisation, WMH can be separated into periventricular and deep. Although both periventricular and deep white matter hyperintensities have been associated with vascular disease [1], it remains to be elucidated whether the WMH subtypes are most strongly associated with large vessel disease, small-vessel disease, or thrombo-embolic disease. Furthermore, incident MRI-defined cerebral infarcts commonly affect the elderly. Most are small, subcortical, and not associated with acute symptoms. Since these silent infarcts have been associated with WMH, they may share a common pathophysiology [3 5].

Direct evidence of ischemia associated with incidental WMH is lacking. A recent population-based, post-mortem cohort of 456 donated brains was examined by MRI and histology [6]. In a subsample of the whole cohort, magnetic resonance images were used to sample and compare WMH and normal appearing WM for molecular markers of hypoxic injury. In that study, periventricular WMH were associated with loss of ventricular ependyma, while deep WMH were associated with arteriolar sclerosis compared with normal white matter. Hypoxia-regulated proteins were increased in all WMH. Other neuro-anatomical studies also suggest a different etiology of periventricular and deep WMH, but the definition of periventricular an deep WMH differed between these studies, making it difficult to compare [7-10].

High volumes of total WMH in the brain have been described as a predictor of small, deep cerebral infarcts [11]. This increased risk is independent of traditional risk factors for stroke. Findings from the Rotterdam Scan Study indicate that subjects with periventricular WMH have a 4.7 fold increased risk of silent brain infarcts and that subjects with subcortical WMH have a 3.6 fold risk [12]. The association between WMH and silent brain infarcts supports the concept of small-vessel disease underlying these two phenomena. The aim of our study was to explore the

longitudinal association of periventricular and deep WMH with subtypes of cerebral infarcts in order to learn more about possible, shared pathways.

Methods

All subjects of this MRI study participated in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) study [13, 14]. The Prosper study was a double blind, randomized, placebo controlled trial, examining the effect of pravastatin 40 mg on ischemic heart disease, stroke and cognitive decline in 5804 men and women, all aged 70-82 years, with vascular disease or at high vascular risk. Characteristics of this MRI study have been published elsewhere [15]. In short, a total of 554 subjects underwent MRI of the brain at baseline and follow-up. The interval between baseline and follow-up MRI was 33 ± 1.4 (mean ± SD) months. For the analysis of this study 533 subjects were included, consisting of 302 men and 231 women. The LUMC institutional ethic review board approved the protocol for the Prosper study, including the MRI substudy, and all participants gave written informed consent.

MRI was performed on a system operating at 1.5 T field strength (Philips Medical Systems, Best, The Netherlands). We obtained dual fast spin echo images, fluid attenuated inversion recovery (FLAIR) images and susceptibility-weighted scans of all subjects at baseline and follow up. MRI parameters were the following for dual fast spin echo: time to echo (TE) 27/120 ms, time to repeat (TR) 3000 ms, echo train length factor 10, 48 contiguous 3 mm slices, matrix 256x256, field of view (FOV) 220, for FLAIR: TE 100 ms, TR 8000 ms, 48 continuous 3 mm slices, matrix 256x256, FOV 220, and for susceptibility-weighted scan: TE SH(48) ms, TR SH(2593) ms, 22 slices, matrix 256x256, FOV 220.

Segmentation of WMH was assessed from the dual echo MR images, using in-house developed, semi-automated lesion detection software [16]. For segmentation and quantification of the WMH, the images were transferred to an off-line workstation. Segmentations of WMH volumes were generated automatically, by combining fuzzy clustering, connectivity rules and mathematical morphology. WMH were defined as hyperintense lesions on both Proton Density and T2-weighted

images. Lesions connected to the lateral ventricles were labelled as periventricular WMH. Inferior and superior boundaries of periventricular WMH were within two slices before the first and after the last exhibit of the lateral ventricles. WMH not connected to the lateral ventricles were labelled as deep WMH. WMH were subsequently edited and reviewed manually by two trained raters to correct for misclassification (i.e. grey matter, Virchow-Robin spaces, cerebro-spinal fluid.[15 17] Cerebral infarcts and the surrounding rim were not included in the WMH volume.

Cerebral infarcts on baseline and follow-up scans were identified on FLAIR hard copies by three experienced neuroradiologists. All scans were analyzed in pairs. A cerebral infarct was defined as a parenchymal defect, with the same signal intensity as CSF and following a vascular distribution. There should be no mass effect. Hemorrhagic infarcts and bleedings were detected and excluded based on the presence of hemosiderin in the wall of the parenchymal defect on the susceptibility-weighted scan. We distinguished two different types of cerebral infarcts. Infarcts with any cortical involvement were defined as cortical infarcts. All other infarcts were defined as subcortical infarcts.

We used nonparametric Mann-Whitney U tests to assess the cross-sectional association between presence of cerebral infarcts at baseline and volume of WMH. Analysis of the association between presence of WMH at baseline and new cerebral infarcts during follow-up was done with logistic regression. In all logistic regression analyses volume of WMH was dichotomized around the median and all odd ratios were corrected for age, sex, presence of baseline cerebral infarct, and use of pravastatin. P-values < 0.05 were considered statistically significant. Statistical analysis was performed with SPSS, version 12.0.

Results

Baseline characteristics of participants are shown in table 1. Average age was 75 years, with 313 men and 241 women. Almost 50% of participants had a history of a vascular event, while 16% had a history of stroke or transient ischemic attack.

Volumes of total, periventricular, and deep WMH were not associated with cortical infarcts at baseline (all p-values > 0.1, table 2), but were strongly associated with

presence of subcortical infarcts at baseline (all p-values < 0.001). A total of 22 subjects had at least one cortical infarct and at least one subcortical infarct at baseline. When we excluded those 22 subjects from the analysis, the results did not change.

During follow-up, 24 subjects had developed at least one new cortical infarct and 62 subjects had developed at least one new subcortical infarct. A high volume of total, periventricular, or deep WMH at baseline was not predictive for new cortical infarcts during follow-up (table 3). However, a high volume of total WMH at baseline predicted the occurrence of subcortical infarcts during follow-up (OR 4.6, 95% CI 1.9-10.9). The increased incidence of subcortical infarcts was mainly attributable to the periventricular WMH (OR 4.6, 95% CI 2.0-10.8) and not to the deep WMH (OR 1.7, 95% CI 0.9 – 3.9). Eight subjects had developed both a cortical and a subcortical infarct. When we excluded those eight subjects from the analysis, the results did not change.

Discussion

In our study, elderly subjects with subcortical infarcts at baseline had higher volumes of total, periventricular, and deep WMH at baseline compared with subjects without subcortical infarcts. Subjects with cortical infarcts did not have higher volumes of any WMH compared with subjects with no cortical infarcts. Moreover, high baseline volume of periventricular WMH, and not deep WMH, was predictive for subcortical infarcts during follow-up.

Until now, most studies relating WMH to cerebral infarcts have measured total WMH and did not separate this into periventricular and deep [5, 18]. These studies showed that a high grade of WMH predicted cerebral infarcts. Other studies have shown that total WMH predicts mainly one subtype of cerebral infarcts, e.g. lacunar infarcts [11 19]. The Rotterdam Scan Study was the first study which investigated the association between subtypes of WMH and cerebral infarcts. They found periventricular as well as deep WMH to be a predictive for silent cerebral infarcts. Contrary to their results, we found only periventricular and not deep WMH to be a predictor of subcortical infarcts. This difference might be explained by the rating

method of cerebral infarcts. In the Rotterdam Scan Study, the association between subtypes of WMH with silent cerebral infarcts was investigated, where cerebral infarcts were not divided into cortical and subcortical infarcts. In our study we found no association between any subtype of WMH with cortical infarcts. Because of this difference in scoring cerebral infarcts, the results of the Rotterdam Scan Study and our study can not easily be compared.

We have shown earlier that a decline of total cerebral blood flow is associated with an increase of periventricular and not deep WMH [20]. This suggests that periventricular WMH might be caused by diffuse perfusion disturbance, as measured by a decline in total cerebral blood flow, while deep WMH might more likely be caused by local perfusion disturbances because of occlusion of incidental, small vessels. Moreover, periventricular WMH are typically located symmetrically in both cerebral hemispheres, which might also be suggestive for diffuse perfusion disturbance. On the contrary, deep WMH are often smaller and frequently have an asymmetrical distribution over both hemispheres which might be suggestive for local perfusion disturbances. In our study we showed that high baseline volume of periventricular WMH predicted occurrence of subcortical infarctions. Combining these observations, we suggest that a decline of total cerebral blood flow might result in progression of periventricular WMH and that these periventricular WMH predict occurrence of subcortical infarctions. This supports the hypothesis of a shared, pathophysiologic pathway of periventricular WMH and subcortical infarcts.

Our study indicates a different etiology of periventricular and deep WMH. Cortical infarcts mainly result from cardiac embolism or artery-to-artery embolism from the carotid artery [11]. In our study, cortical infarcts were not associated with WMH, hence cardiac embolism or artery-to-artery embolism from the carotid artery is not a likely cause of WMH. The association of periventricular WMH with subcortical cerebral infarcts suggests that periventricular WMH are primarily related to diffuse small-vessel disease rather than large-artery or thrombo-embolic disease. Lipohyalinosis (arteriolosclerosis), produced by chronic hypertension, is thought to be an important pathological process altering small-vessels [21]. Neuro-anatomical studies suggest that periventricular and deep WMH indeed have a different etiology

[6-10]. The development of periventricular WMH has been attributed to arteriosclerosis and lipohyalinosis of the long penetrating arteries in combination with impaired autoregulation which may result in hypoxia of the periventricular white matter [7]. Also, collagenous thickening of the periventricular-draining veins, loss of the ventricular ependyma, and breakdown of the blood-brain barrier are suggested as mechanisms in the development of periventricular WMH [6-8]. Deep WMH are thought to be caused by fibrohyalinosis or also lipohyalinosis [6, 8]. Further studies focussing on the etiology of WMH are needed to clarify this issue.

In conclusion, we found supporting evidence for a different etiology of periventricular and deep WMH. Moreover, we found that periventricular WMH and subcortical brain infarcts might share a similar underlying pathophysiology. Further studies are needed to clarify the pathophysiology of this diffuse, small-vessel disease.

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Table 1: Baseline characteristics

	PROSPER MRI Study (N=554)
Continuous data (mean, SD)	
Age (years)	75.0 (3.2)
Systolic blood pressure (mmHg)	157.5 (21.7)
Diastolic blood pressure (mmHg)	85.8 (11.0)
Total cholesterol (mmol/L)	5.75 (0.85)
LDL cholesterol (mmol/L)	3.86 (0.74)
HDL cholesterol (mmol/L)	1.24 (0.32)
Triglycerides (mmol/L)	1.49 (0.67)
Categorical data (n, %)	
Male	313 (56.5)
Current smoker	115 (20.8)
History of diabetes	91 (16.4)
History of hypertension	350 (63.2)
History of myocardial infarction	67 (12.1)
History of stroke or transient ischemic attack	90 (16.2)
History of any vascular disease	241 (43.5)

Table 2: Baseline volume of white matter hyperintensities in subjects with and without cortical and subcortical infarcts.

	Volume of WMH (cm^3)		
Type of infarct	Total	Periventricular	Deep
Cortical			
Present (n=31)	2.2 (1.0-6.9)	1.1 (0.5-6.3)	0.7 (0.2-1.2)
Absent (n=502)	1.7 (0.5-5.7)	1.0 (0.2-4.0)	0.5 (0.1-1.5)
p-value	0.13	0.19	0.29
Subcortical			
Present (n=153)	4.2 (1.4-9.5)	3.1 (0.7-7.3)	1.0 (0.3-1.9)
Absent (n=380)	1.1 (0.3-3.9)	0.7 (0.2-2.8)	0.3 (0.1-1.1)
p-value	<0.001	<0.001	<0.001

Volume of WMH is presented as median with interquartile range.

WMH= white matter hyperintensities.

Table 3: Volume of white matter hyperintensities at baseline and incidence of cortical and subcortical infarcts during follow-up

	Cortical infarct			Subcortical infarct		
Type of WMH	OR	95% CI	p-value	OR	95% CI	p-value
Total	2.1	0.7-6.4	0.19	4.6	1.9-10.9	0.001
Periventricular	2.2	0.7-6.7	0.17	4.6	2.0-10.8	<0.001
Deep	1.5	0.5-4.4	0.46	1.9	0.9-3.9	0.07

White matter hyperintensities were dichotomized around the median. Data were corrected for age, sex, baseline infarct, and use of pravastatin.

WMH= white matter hyperintensities.