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Accelerated progression of white matter hyperintensities and subsequent risk of mortality: a 12-year follow-up study

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ABSTRACT

We examined the association of accelerated progression of white matter hyperintensities (WMH) with mortality outcomes in 534 older subjects at risk for cardiovascular disease. Using brain magnetic resonance imaging, volume of WMH was measured 2 times in an average of 33 months apart. After the second magnetic resonance imaging, occurrence of death was recorded during 12 years of follow-up. In multivariable analyses, each mL/y increase in global WMH was associated with 1.22-fold (95% confidence interval [CI], 1.09–1.37) higher risk of all-cause mortality, 1.29-fold (95% CI, 1.06–1.56) higher risk of cardiovascular mortality, and 1.20-fold (95% CI, 1.02–1.40) higher risk of noncardiovascular mortality. Each mL/y increase in periventricular WMH was associated with 1.22-fold (95% CI, 1.08–37) higher risk of all-cause mortality and 1.24-fold (95% CI, 1.06–1.44) higher risk of noncardiovascular mortality. Conversely, deep cortical WMH was only associated with cardiovascular mortality (1.92-fold, 95% CI, 1.12–3.30). Accelerated progression of WMH is linked with mortality risk in old age. Progression of periventricular WMH associates with noncardiovascular mortality, whereas progression of deep cortical WMH associates with cardiovascular mortality.

1. Introduction

White matter hyperintensities (WMH) are commonly observed on brain magnetic resonance imaging (MRI) of older subjects (Soderlund et al., 2003). Neuroimaging studies have shown that about 80 percent of older people from the general population have deep cortical WMH and >60 percent have periventricular WMH (de Leeuw et al., 2001). Increasing evidence supports that higher loads of WMH are associated with adverse health outcomes (Debette and Markus, 2010). Despite this evidence and given that prevalent WMH might basically reflect long-term vascular and inflammatory insults to the brain (Raz et al., 2012), it is unknown whether rapid progression of WMH in old age is also associated with higher risk of mortality.

Previous studies have reported different neuropathological features for periventricular and deep cortical WMH and also showed that location of WMH is related to various clinical consequences (Kim et al., 2008). For instance, periventricular (and not deep cortical) WMH is associated with impaired executive function and processing speed (Seo et al., 2012), whereas subjects with depression have higher loads of deep cortical WMH (Sheline et al., 2008). Studies on the association between WMH and mortality have mainly focused on total WMH, and it is unclear whether progression of WMH in different anatomical locations shows differential association in relation to all-cause, cardiovascular, and noncardiovascular mortality.

In this study, in a cohort of older subjects at risk for cardiovascular disease, we investigated whether rapid progression of WMH is linked with a higher risk of all-cause, cardiovascular, and noncardiovascular mortality. Furthermore, we tested whether periventricular and deep cortical WMH show different associations in relation to mortality outcomes.

2. Methods

2.1. Setting and participants

We included participants from the nested MRI substudy of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), a randomized clinical trial investigating the benefits of pravastatin on

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Table 1
Baseline characteristics of study participants in relation to WMH progression

Characteristics	All (n = 534)	Tertiles of total WMH progression			
		Low (n = 178)	Middle (n = 178)	High (n = 178)	*p*-value[a]
WMH progression					
Total, mL/y, median (IQR)	0.20 (0.01, 0.72)	0 (−0.04, 0.02)	0.23 (0.11, 0.35)	1.05 (0.71, 1.60)	
Periventricular, mL/y, median (IQR)	0.20 (0, 0.72)	0 (−0.04, 0.01)	0.22 (0.10, 0.35)	1.04 (0.70, 1.60)	
Deep cortical, mL/y, median (IQR) l	0.05 (0, 0.16)	0 (−0.01, 0.01)	0.07 (0.01, 0.12)	0.21 (0.06, 0.45)	
Sociodemographic factors					
Age, y, mean (SD)	74.5 (3.2)	73.7 (3.0)	74.5 (3.2)	75.2 (3.2)	<0.001
Men, n (%)	312 (56.4)	109 (61.2)	99 (55.6)	94 (52.8)	0.263
Age left school, y, mean (SD)	15.4 (2.9)	15.4 (2.9)	15.4 (2.7)	15.7 (3.0)	0.603
Current smoker, n (%)	115 (20.8)	33 (18.5)	38 (21.3)	40 (22.5)	0.642
Cardiovascular factors					
History of CVD, n (%)	240 (43.4)	66 (37.1)	78 (43.8)	85 (47.8)	0.120
History of stroke or TIA, n (%)	89 (16.1)	21 (11.8)	29 (16.3)	33 (18.5)	0.202
History of CAD, n (%)	67 (12.1)	26 (14.6)	21 (11.8)	19 (10.7)	0.510
Serum cholesterol, mmol/L, mean (SD)	5.7 (0.8)	5.7 (0.8)	5.8 (0.9)	5.7 (0.8)	0.182
Body mass index, kg/m^2, mean (SD)	26.7 (3.6)	26.7 (3.5)	26.9 (3.8)	26.5 (3.6)	0.685
Diabetes mellitus, n (%)	91 (16.5)	39 (21.9)	24 (13.5)	28 (15.7)	0.091
Antihypertensive therapy, n (%)	349 (63.1)	104 (58.4)	118 (66.3)	116 (65.2)	0.250
Statin treatment, n (%)	275 (49.7)	96 (53.9)	85 (47.8)	90 (50.6)	0.498
SBP, mmHg, mean (SD)	158 (22)	156 (22)	158 (22)	158 (21)	0.578
DBP, mmHg, mean (SD)	86 (11)	86 (11)	86 (11)	86 (10)	0.980
Cognitive function					
MMSE, mean (SD)	28.2 (1.5)	28.2 (1.4)	28.3 (1.5)	28.1 (1.6)	0.317

Key: CAD, coronary artery disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; IQR, inter quartile range; MMSE, Mini-Mental State Examination; SBP, systolic blood pressure; SD, standard deviation; TIA, transient ischemic attack; WMH, white matter hyperintensities.
[a] Probability values indicate significant difference in tertiles of progression in white matter hyperintensities.

vascular outcomes (Shepherd et al., 1999). Study participants were males or females aged 70–82 years with either pre-existing vascular diseases or with increased risk of vascular disease because of smoking, hypertension, or diabetes mellitus. Subjects with congestive heart failure (New York Heart Association class III/IV), significant arrhythmia, and cognitive impairment (Mini-Mental Score Examination score <24) were not recruited in the PROSPER study. Inclusion and exclusion criteria of the PROSPER study have been described in detail elsewhere (Shepherd et al., 1999). A total of 554 Dutch participants who completed the trial underwent 2 successive MRI scans of the brain. The first MRI was during the placebo lead-in period and the second MRI after an average follow-up of 33 months (range: 35–44 months). In this study, we did not include 20 participants from the MRI substudy who had incomplete data for baseline and/or follow-up WMH. There was no significant difference between characteristics of the included participants and subjects with missing values. Because we previously reported that treatment with pravastatin does not influence WMH changes (ten Dam et al., 2005) and accelerated progression of total, subcortical and periventricular WMH were not related to pravastatin use (Supplementary Table 1), participants were included from both pravastatin and placebo groups. In addition, analyses were adjusted for statin treatment. The institutional review board approved the protocol for the MRI study, and all participants gave written, informed consent.

2.2. MRI scanning

All imaging was performed on an MR system operating at field strength of 1.5 T (Philips Medical Systems, Best, the Netherlands). Dual fast spin echo (repetition time [TR] = 3000 ms; echo time [TE] = 27/120 ms; flip angle = 90°; slice thickness = 3 mm; 48 slices; no interslice gap; field of view [FOV] = 220 × 220 mm; matrix = 256 × 204), fluid-attenuated inversion recovery (FLAIR; TR = 8000 ms; TE = 100 ms; flip angle = 90°; slice thickness = 3 mm; 48 slices; no interslice gap; FOV = 220 × 176 mm; matrix = 256 × 153), and susceptibility-weighted images (multislice gradient echo sequence; TR = 2593 ms; TE = 48 ms; flip angle = 60°; slice thickness = 6 mm; 22 slices; interslice gap = 6 mm; whole brain coverage; FOV = 220 × 198 mm; matrix = 256 × 176) were obtained from all subjects. The SIENAX (Structural Image Evaluation, using Normalization, of Atrophy for cross-sectional measurement) technique was used to obtain estimates of total brain parenchymal volume, gray matter and white matter volume. In summary, SIENAX starts by extracting brain and skull images from the single whole-head input data. The brain image is then affine-registered to Montreal Neurological Institute 152 space (by using the skull image to determine the registration scaling), done primarily to obtain the volumetric scaling factor to be used as normalization for head size (Smith et al., 2004). Segmentation of WMH volume was performed automatically using Software for Neuro-Image Processing in Experimental Research, an in-house developed program for image processing (Admiraal-Behloul et al., 2005). This segmentation was based on the T2-weighted and FLAIR images. WMH were defined as hyperintense lesions on both proton density and T2-weighted images. WMH connected to the lateral ventricles were labeled as periventricular WMH, and those not connected to the lateral ventricles were labeled as deep WMH. To correct for incidental inclusion of cerebrospinal fluid and gray matter, the automatically generated WMH segmentations were edited manually by 2 trained raters. Moreover, FLAIR hardcopies were used as a reference to rule out other pathogenesis. To prevent the possibility of over-reading WMH progression in a direct scan comparison setting, we analyzed the first and second MRIs in random order. Fifteen MRI scans were segmented twice to assess the intrarater and inter-rater reliability of the volumetric WMH measurements. Intraclass correlation coefficients for periventricular and deep WMH volumes were all 0.99 (van den Heuvel et al., 2006). Rate of the progression of WMH was calculated by subtracting WMH volumes in the baseline session from WMH in the follow-up session divided by the years between 2 MRI assessments (mL/y).

2.3. Mortality

After the second MRI, participants were followed for occurrence of mortality until January 1, 2012 in a follow-up period of 12 years.