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Relationship between Orthostatic Hypotension and White Matter Hyperintensity Load in Older Patients with Mild Dementia

Hogne Soennesyn[1,7]*, Dennis W. Nilsen[2,3], Ketil Oppedal[1,4], Ole Jacob Greve[5], Mona K. Beyer[6], Dag Aarsland[1,8]

1 Centre for Age-Related Medicine, Stavanger University Hospital, Stavanger, Norway, 2 Department of Cardiology, Stavanger University Hospital, Stavanger, Norway, 3 Institute of Medicine, University of Bergen, Bergen, Norway, 4 Department of Electrical Engineering and Computer Science, University of Stavanger, Stavanger, Norway, 5 Department of Radiology, Stavanger University Hospital, Stavanger, Norway, 6 Department of Radiology and Nuclear Medicine, Oslo University Hospital, Oslo, Norway, 7 MoodNet Research Group, Stavanger University Hospital, Stavanger, Norway, 8 Department of Neurobiology, Ward Sciences and Society, Alzheimer's Disease Research Centre, Karolinska Institute, Stockholm, Sweden

Abstract

Background/Objectives: White matter hyperintensities (WMH) in magnetic resonance imaging (MRI) scans of the brain, and orthostatic hypotension (OH) are both common in older people. We tested the hypothesis that OH is associated with WMH.

Design: Cross-sectional study.

Setting: Secondary care outpatient clinics in geriatric medicine and old age psychiatry in western Norway.

Participants: 160 older patients with mild dementia, diagnosed according to standardised criteria.

Measurements: OH was diagnosed according to the consensus definition, measuring blood pressure (BP) in the supine position and within 3 minutes in the standing position. MRI scans were performed according to a common protocol at three centres, and the volumes of WMH were quantified using an automated method (n = 82), followed by manual editing. WMH were also quantified using the visual Scheltens scale (n = 139). Multiple logistic regression analyses were applied, with highest vs. lowest WMH quartile as response.

Results: There were no significant correlations between WMH volumes and systolic or diastolic orthostatic BP drops, and no significant correlations between Scheltens scores of WMH and systolic or diastolic BP drops. In the multivariate analyses, only APOEε4 status remained a significant predictor for WMH using the automated method (p = 0.037, OR 0.075 (0.007–0.851)), whereas only age remained a significant predictor for WMH scores (p = 0.019, OR 1.119 (1.018–1.230)).

Conclusion: We found no association between OH and WMH load in a sample of older patients with mild dementia.

Introduction

White matter hyperintensities (WMH) are commonly found in cerebral T2-weighted magnetic resonance imaging (MRI) scans in older people [1,2]. WMH seem to have a common distribution regardless of underlying diagnosis [3–4], with a preference for areas of lower relative perfusion. They have been associated with depression [5] and dementia [6]. WMH predict functional decline in voiding, mobility and cognition, and depression [7–9].

WMH have been associated, although only modestly [10], with classic cardiovascular risk factors [2,11] including hypertension [12] and APOEε4 [13], and are considered a marker of

cerebrovascular disease. Alternatively, WMH may, at least in Alzheimer's disease (AD), primarily be associated with neurodegenerative disease [14]. However, some studies [15–19] suggest that hypotension, including orthostatic hypotension, plays a role in the development of WMH.

Orthostatic hypotension (OH) [20] is common in older people [21], and particularly in older people with dementia [22,23]. OH is associated with falls [24], coronary heart disease and increased mortality [25].

Furthermore, one older study using CT scans found seated systolic blood pressure (BP) below 130 to be predictive of having white matter low attenuation (equivalent to WMH in MRI) of the

brain [26], suggesting that the absolute BP level might be of importance.

In this study we wanted to explore the association between OH and WMH in older people with mild dementia. We hypothesized that systolic and/or diastolic BP drop at baseline are positively correlated with total WMH volumes and Scheltens deep WMH scores, and that having OH, or standing systolic BP at or below 110 mm Hg at baseline is independently associated with having more severe WMH on imaging. Since OH appears to be particularly common in Lewy body dementias [27], we tested this association separately.

Methods

Subjects

Consecutive referrals to dementia clinics in the counties of Rogaland and Hordaland in western Norway from March 2005 to March 2007 were screened, and patients with a first time diagnosis of mild dementia, i.e. a minimum Mini-Mental State Examination (MMSE) score of 20 were included. From April 2007 we selectively recruited patients with dementia with Lewy bodies (DLB) and Parkinson's disease with dementia (PDD) fulfilling the aforementioned criteria of mild dementia. A total of 246 patients have completed baseline assessments, the last of whom was included in May 2011. In the current study, we included those who had both OH measurements and available MRI scans with adequate scan quality.

Ethics Statement

The study was approved by the Regional Committee for Medical Research Ethics, Western Norway and the Norwegian authorities for collection of medical data. The subjects provided written consent to participate after the study procedures had been explained in detail to them and a caregiver, usually the spouse or offspring.

Dementia Diagnosis

The diagnoses for AD, DLB, PDD and vascular dementia (VaD) were made according to consensus criteria [28–31], and for frontotemporal dementia (FTD) and alcoholic dementia according to the Lund-Manchester criteria [32] and the DSM-IV criteria, respectively. DLB and PDD were combined into one group (Lewy body dementia, LBD), because these conditions have several clinical and biological similarities [29,33].

The diagnostic procedures and comprehensive standardised assessment have been described elsewhere [34]. Patients with acute delirium or terminal illness, as well as those recently diagnosed with a major somatic illness, previous bipolar disorder or psychotic disorder were excluded.

Blood Pressure Measurements

Blood pressures were measured at baseline only, using an analogue sphygmomanometer. The protocol did not require a period of rest prior to the BP measurements. In the majority of patients, BP was measured once with the subject in the supine position, and then once (all patients) within 3 minutes after standing up. In some patients, the non-standing BP measurements were made in the sitting position (22/80 in the volumetry group, and 60/134 in the semi-quantitative group). For n = 9 patients the non-standing position is unknown.

Orthostatic hypotension (OH) was defined according to the consensus as a reduction of systolic BP of at least 20 mm Hg or diastolic BP of at least 10 mm Hg within 3 minutes of standing

[20]. The diagnosis of OH was based solely on the baseline BP measurements.

By contrast, a diagnosis of hypertension was based on the medical history and the medical records only, and not on the baseline BP measurements.

The assessments took place during normal office hours (i.e. 8 a.m. to 4 p.m.).

APOE

Apolipoprotein E (APOE) genotypes were determined in a subgroup. First, genomic DNA was extracted from 200 µl EDTA-blood using the QIAamp 96 DNA Blood Kit (Qiagen, Hilden, Germany). For detection of the APOE ε2, ε3 and ε4 genotypes, which are determined by the combination of two SNP's (rs7412 and rs429358), we employed the LightCycler APOE Mutation Detection Kit (Roche Diagnostics, Mannheim, Germany), using the assay according to the instructions of the manufacturer.

Assessment of Physical Comorbidity

We employed the "Cumulative Illness Rating Scale" (CIRS) for assessment of physical comorbidity. This instrument measures the chronic medical illness burden, while also taking into account the severity of chronic diseases. Scoring was done by an experienced geriatrician, in accordance with guidelines [35].

MRI

Patients were scanned at three different sites; Stavanger University Hospital, Haugesund Hospital, and Haraldsplass Deaconess Hospital (Bergen). 1.5 T scanners were used in all three centres (Philips Intera in Stavanger and Haugesund, and in Bergen a 1.5T GE Signa Excite scanner). In each centre, MRI was done on the same scanner during the entire study period, and a common study imaging protocol was used. For technical details, see Soennesyn et al. [9]. A phantom study, using the same three scanners, of three human volunteers was done for the DemWest study and has recently been published [36]. This was done to assess the variability between scanners and also to assess intra-scanner variability. Cronbach's alpha between the three MRI scanners, as well as between two points in time, all exceeded 0.95, indicating excellent reliabilities.

The MRI scans were performed within a median interval of 2 months (interquartile range 1–4 months) from the baseline clinical examination.

Volumetric assessment of WMH. Image analysis was performed according to a method developed and previously published by Firbank et al. [4] and modified as previously described [9]. Briefly, this method requires sets of 3DT1 weighted scans and FLAIR images from each patient. Non-brain regions were removed from the T1 image, and the WMH were segmented on a slice-by-slice basis from the FLAIR image, using a threshold determined from the histogram of pixel intensities for each image slice. An MNI atlas image registered to the FLAIR image was used to calculate the WMH volumes in different regions of the brain.

Because of the variability in image quality from the different centres participating in this study, we found it difficult to empirically choose a single threshold level that gave us a perfect segmentation result in each subject. Therefore, a threshold level of 1.2 was chosen, by which the lesion load was overestimated. Later, manual correction was performed by removing excess pixels using FSLView (http://www.fmrib.ox.ac.uk/fsl/index.html).

A specialist in internal medicine and geriatrics (HS) performed the manual editing, blind to clinical data, after training by a consultant neuroradiologist (MKB). They both edited the same

10 datasets twice; once in the beginning, to secure good inter-rater reliability, and a second time at the end of the editing process, to secure that similar reliability still persisted and to evaluate intra-rater reliability. The intraclass correlation coefficient (ICC) was calculated to be 0.998 for inter-rater reliability and 0.964 for intra-rater reliability. The manually edited scans were then used in the further analyses of volumes of total and regional WMH. In order to compensate for interindividual differences in total brain volumes, we calculated the ratios of volumes of WMH to total brain volumes, using these in the statistical analyses. In the present study, we used only the ratios of total WMH volumes, which have been shown to be highly correlated with regional WMH volumes [37].

Visual assessment of WMH. MRI's were also rated visually, using the Scheltens scale [38], by an experienced rater (OJG), blind to clinical data. According to the Scheltens scale, white matter changes (WMC) are subdivided into periventricular WMC and deep WMC, and deep WMC are further subdivided into deep WMH (DWMH), basal ganglia WMH (BGH) and infratentorial hyperintensities (IT) [39]. In the statistical analyses, we used only the DWMH scores, because these have been associated with (orthostatic) BP drop in previous studies [15,17]. Inter-rater reliability with another experienced rater (MKB) was evaluated, based on 12 scans, finding an ICC of 0.923.

Statistical Analyses

A total of 82 patients had MRI scans that could be analysed volumetrically (volumetry group), and 139 had scans that could be rated semi-quantitatively (the semi-quantitative group) according to the Scheltens scale. The scans of 61 patients were analysed with both methods, yielding a correlation coefficient (Spearman's rho) of 0.791 ($p<0.001$) between the scores of the two methods. Mann-Whitney U-test, Chi-square, Spearman rank order or Fisher's exact test were used as appropriate. None of the continuous variables had a normal distribution, according to the Kolmogorov-Smirnov test.

Potential predictor variables having p-values <0.25 in bivariate logistic regression analyses were included in stepwise multiple logistic regression analyses, with the response variable defined as being in the highest quartile of total WMH volume ratios or Scheltens deep WMH (DWMH) scores vs. the lowest quartile, respectively.

P-values <0.05 (two-tailed) were considered statistically significant.

All statistical tests were performed using PASW Statistics 18, release 18.0.1.

Results

When comparing the baseline characteristics of patients undergoing WMH volume analysis with those who were not included in the study, the only significant difference was a higher proportion with Alzheimer's disease among the participants (volumetry group: Pearson Chi square 14.558, df 1, $p<0.001$, semi-quantitative group: Pearson Chi square 8.162, df 1, $p = 0.006$ (Table 1)).

In the volumetry group, the only significant difference with respect to relevant clinical characteristics between patients in the highest and lowest WMH quartiles was a lower proportion in the former group with at least one APOEε4 allele (Table 2).

In the semi-quantitative group, patients in the highest DWMH score quartile were significantly older than those in the lowest quartile, and the proportion of patients with a previous stroke was significantly higher in the highest quartile. Otherwise, there were

no significant differences between those belonging to the highest and lowest DWMH score quartiles.

We did not find any significant association between a history of hypertension and having OH at baseline (Pearson Chi Square 0.224, df 1, $p = 0.636$).

Associations between WMH and OH

There was no significant correlation between WMH volume ratios and the systolic orthostatic BP drops (Spearman's rho 0.022, $p = 0.848$), but a trend with diastolic orthostatic BP drops was demonstrated (Spearman's rho -0.213, $p = 0.066$). Similarly, we found no significant correlations between DWMH scores and systolic or diastolic orthostatic BP drops (Spearman's rho 0.037, $p = 0.700$ and Spearman's rho -0.122, $p = 0.202$, respectively).

We performed bivariate logistic regression analyses with the variables in Table 2 as predictors, and being in the highest WMH quartile vs. the lowest quartile as response variable. In the volumetry group, age, hypertension, coronary heart disease and APOEε4 status had p-values <0.25. As to the semi-quantitative group, age, hypertension, APOEε4 status and previous stroke had p-values <0.25. None of the p-values for the BP variables approached this level, except diastolic BP drop vs. DWMH score ($p = 0.297$). The aforementioned variables having p-values <0.25 were entered into stepwise multiple logistic regression analyses.

In the final model, only APOEε4 status remained a significant predictor of the volumes of WMH (Table 3). The model performed well (Omnibus test of model coefficients $p<0.05$), and the model fit was good (Generalised linear models, Pearson Chi Square $p = 0.179$). Only age remained a significant predictor of DWMH scores (Table 4). The model performed well (Omnibus test of model coefficients $p = 0.010$), and the model fit was good (Hosmer and Lemeshow test $p = 0.492$).

We also performed multiple logistic regression analyses (stepwise and forced entry) controlling for scanning site and including variables known from previous studies to be associated with WMH (age, hypertension, diabetes mellitus), in addition to OH or systolic or diastolic BP drops. In these analyses, both with respect to the volumetry group and the semi-quantitative group, only age remained a significant predictor of WMH load (data not shown). However, in some of the models the predictor "MRI centre" achieved borderline significance ($p = 0.048$–0.050).

When analysing the patients with DLB/PDD separately, we found no significant correlations between Scheltens DWMH scores and systolic or diastolic BP drops. Similarly, there were no significant differences between those in the highest and lowest Scheltens DWMH score quartiles with respect to the other variables in Table 2 (data not shown). In bivariate logistic regression analyses, diastolic BP drop, age and APOEε4 status achieved the lowest p-values (0.124, 0.117 and 0.094, respectively). Due to the rather small subsample, in combination with missing values for the relevant variables, it was not statistically feasible to perform multiple logistic regression analyses using these variables.

Discussion

The main finding of our study is that in this sample of older people with mild dementia, WMH were not associated with OH or low standing systolic BP. Only APOEε4 status (volumetry) and age (volumetry and semi-quantitative analysis) were independently associated with WMH volumes.

Thus, our hypothesis that WMH in mild dementia are associated with OH was not supported. This finding is in contrast to some previous studies. However, some of these studies were performed in older people with major depression [16,18,19],

Table 1. Demographic and clinical characteristics.

	Total sample n = 246	Volumetry group (n = 82), vs. rest of sample	Semi-quantitative group (n = 139), vs. rest of sample	Missing data (out of n = 246)
Age, median (IQR)	76.9 (71–81)	76.1 (70–81), p = 0.502	76.5 (71–81), p = 0.562	0
Women, n (%)	139 (57)	51 (62), p = 0.256	84 (60), p = 0.198	0
MMSE, median (IQR)	24 (22–26)	24 (22.5–26), p = 0.217	23.3 (22–25), p = 0.377	5
Coronary heart disease, n (%)	49 (21)	15 (19), p = 0.704	27 (21), p = 0.949	16
Hypertension (history of), n (%)	109 (46)	30 (38), p = 0.115	63 (47), p = 0.831	11
Diabetes mellitus, n (%)	21 (9)	9 (11), p = 0.495	10 (7), p = 0.455	12
APOEε4≧1 allele, fractions (%)	93/153 (61)	31/53 (59), p = 0.803	61/98 (62), p = 0.748	93
Previous stroke, n (%)	33 (14)	8 (10), p = 0.302	18 (14), p = 0.960	14
Smoker (former/pres.), n (%)	111 (48)	37 (47), p = 0.862	62 (48), p = 0.949	16
Heart failure, n (%)	12 (5)	2 (3), p = 0.227	5 (4), p = 0.416	22
Orthostatic hypotension (present), n (%)	90 (46)	35 (47), p = 0.945	49 (44), p = 0.727	49
CIRS score, median (IQR)	6 (4–8)	6 (4–7), p = 0.402	6 (4–7), p = 0.780	10
No. of drugs, median (IQR)	4 (2–6)	4 (2–5), p = 0.159	4 (2–5), p = 0.466	11
Blood pressure lowering medication*, n (%)	141 (60)	41 (53), p = 0.167	77 (57), p = 0.361	9
Dementia categories		**p = 0.000**	**p = 0.002**	0
Alzheimer's disease, n (%)	138 (56)	60 (73)	89 (64)	
DLB/PDD, n (%)	89 (36)	16 (20)	38 (27)	
Vascular dementia, n (%)	11 (4)	2 (2)	5 (4)	
FTD/alcoholic dem., n (%)	8 (3)	4 (5)	7 (5)	

IQR = interquartile range; MMSE = Mini-Mental State Examination, normal range 24–30; AD = Alzheimer's Disease; DLB = Dementia with Lewy Bodies; PDD = Parkinson's Disease Dementia; VaD = vascular dementia; FTD = Frontotemporal Dementia; CIRS = Cumulative Illness Rating Scale, range 0 (no impairment)-52 (extremely severe impairment); APOE = Apolipoprotein E.
*antianginals, antihypertensives, tricyclic antidepressants, paroxetine,MAO inhibitors, dopamine agonists, diazepam, dipyridamole, phenothiazines, clozapine, quetiapine, haloperidol.
Significant results are shown in **bold** typeface.
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whereas in our study only a minority (17%) had clinically significant depression (defined as a Montgomery Asberg Depression Rating Scale [40] score of at least 15). In the other studies [15,17], a majority of the relevant subjects had DLB, known to

Table 2. Demographic and clinical characteristics, lowest vs. highest WMH quartile.

	Volumetry group	Semi-quantitative group
OH (fractions)	10/17, 10/19 p = 0.970	12/25, 14/28 p = 1.000
Systolic BP drop (median)*	10, 10 p = 0.949	10, 17.5 p = 0.492
Diastolic BP drop (median)*	0, 0 p = 0.308	3, 0 p = 0.158
Standing syst. BP≤110 (fractions)	1/17, 2/19 p = 1.000	4/26, 2/28 p = 0.413
Age (median)*	73, 79.5 p = 0.081	72, 78.4 **p = 0.002**
Women (fractions)	15/20, 13/20 p = 0.730	19/37, 17/31 p = 0.966
AD (fractions)	16/20, 14/20 p = 0.715	22/37, 22/31 p = 0.463
Hypertension (fractions)	6/18, 11/20 p = 0.310	10/36, 16/31 p = 0.081
Coronary heart disease (fractions)	1/19, 5/20 p = 0.182	6/35, 7/30 p = 0.756
Diabetes mellitus (fractions)	1/19, 1/20 p = 1.000	3/36, 2/31 p = 1.000
APOEε4≧1 allele (fractions)	11/12, 6/13 **p = 0.030**	17/36, 10/21 p = 0.353
Previous stroke (fractions)	2/20, 4/19 p = 0.407	2/34, 9/28 **p = 0.016**
Smoker (former or present)(fractions)	8/20, 11/20 p = 0.527	19/33, 16/30 p = 0.933
Heart failure (fractions)	0/20, 1/18 p = 0.474	2/34, 1/28 p = 1.000

WMH = white matter hyperintensities; OH = orthostatic hypotension; BP = blood pressure; AD = Alzheimer's disease; APOE = apolipoprotein E.
*Mann-Whitney U-test, all other comparisons Chi-Square or Fisher's Exact test.
Significant results are shown in **bold** typeface.
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Table 3. Multiple logistic regression analysis of the effect of APOEε4 status on likelihood of having WMH volume in highest vs. lowest quartile (final model).

	B	S.E.	p	Odds Ratio Exp. (B) (95% CI)
≥1 APOEε4 allele	−2.595	1.242	0.037	0.075 (0.007–0.851)

APOE = apolipoprotein E; WMH = white matter hyperintensities; CI = confidence interval.
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Table 4. Multiple logistic regression analysis of the effect of age on likelihood of having Scheltens deep WMH score in highest vs. lowest quartile (final model).

	B	S.E.	p	Odds Ratio Exp. (B) (95% CI)
Age (years)	0.112	0.048	0.019	1.119 (1.018–1.230)

APOE = Apolipoprotein E; WMH = white matter hyperintensities; CI = confidence interval.
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have lower standing systolic BP values than AD [23], whereas in our study the majority had AD. Furthermore, in these two last studies blood pressures were measured partly or only during carotid sinus massage, as opposed to our study, in which the blood pressures were measured only in the supine (or sitting) position and during active standing. Subjects with OH according to these two different methods may not be comparable, e.g. concerning the pathophysiology of WMH.

In our study, the presence of at least one APOEε4 allele was associated with reduced odds of having high WMH volume, suggesting that other APOEε alleles (i.e. ε2 and/or ε3) may increase the odds of high WMH volume. This hypothesis is supported by at least two previous studies [41,42]. Notably, none of these included subjects with dementia. Alternatively, patients possessing the ε4 allele may have more neurodegenerative changes and thus develop dementia with a lower WMH load. However, the majority of studies in this field have not demonstrated any association between APOEε4 status and WMH burden [43–48].

In contrast to some previous studies (e.g. [49]), we did not find any significant associations between hypertension and WMH. This could have several possible explanations, including different definitions of hypertension, different study designs, and differences regarding samples.

This being a multicentre study, it is possible that the measured or scored WMH values might vary systematically according to scanning site. The results of the phantom studies, as well as the results of the multivariate analyses including scanning site as a variable, do not support this hypothesis.

The strengths of our study include the use of both quantitative and semi-quantitative methods for evaluation of WMH severity. Furthermore, we had data on a number of potential causal or risk factors for WMH, enabling us to include these in the analyses.

Limitations include the cross-sectional design, the relatively small sample size, and orthostatic BP measurements in a number of cases obtained from the sitting, instead of the supine position. It has previously been demonstrated that sit-stand testing for OH has a very low diagnostic accuracy [50]. However, sit-stand measurement only has been used in recent, similar studies [51,52]. In addition, no standing BP measurements were made after 3 minutes. According to a previous study [53], at least 20–30% of dementia patients have a delayed orthostatic response. Thus, our methodology would tend to underestimate the prevalence of OH, thereby possibly masking the potential association between OH

and WMH. Furthermore, the consensus definition of OH, which was employed in the present study, does not in itself require the orthostatic BP to be measured on more than one occasion. This is a potential limitation, as this approach cannot distinguish those having only transient OH from those having more persistent or frequently recurring OH. The latter groups may have a higher risk of being afflicted with the potential adverse consequences of BP drops, such as syncope and cerebral hypoperfusion, and possibly also the development of WMH. Ideally, in order to identify individuals with more than transient OH, orthostatic blood pressures should have been measured repeatedly over a period of e.g. a few weeks. Moreover, if OH does play a role in the development of WMH in mild dementia, it probably exerts its effects over an extended period of time, also prior to the diagnosis of dementia. Exploring this clearly would require a longitudinal study. One final point is that due to missing data for some variables, a relatively low number of subjects could be included in the multiple logistic regression analyses, thus limiting the number of predictors that could be entered into these analyses, as well as their power.

Our results suggest that OH or low standing BP may not be associated with WMH in older people with mild dementia, at least not cross-sectionally. Instead, these changes may primarily be associated with neurodegenerative disease [14], ageing [54], hypertension and smoking [2,11], genetics [55], or combinations of these factors. However, recent longitudinal studies indicate that an unfavourable vascular risk factor status from midlife and onwards may be of importance for the development of WMH in later life [10,56,57]. Thus, the best opportunities for potential prevention of these changes may lie in controlling established vascular risk factors, starting no later than in midlife.

Conclusion

In a sample of older people with mild dementia, we found no cross-sectional association between OH and WMH load. Future studies should include larger samples, use a longitudinal design, and use more rigorous BP measurement protocols.

Author Contributions

Conceived and designed the experiments: HS DWN DA. Performed the experiments: HS KO OJG MKB. Analyzed the data: HS DA. Wrote the paper: HS DA.

References

1. Ylikoski A, Erkinjuntti T, Raininko R, Sarna S, Sulkava R, et al. (1995) White matter hyperintensities on MRI in the neurologically nondiseased elderly. Analysis of cohorts of consecutive subjects aged 55 to 85 years living at home. Stroke 26: 1171–1177.
2. Breteler MM, van Swieten JC, Bots ML, Grobbee DE, Claus JJ, et al. (1994) Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: the Rotterdam Study. Neurology 44: 1246–1252.
3. Holland CM, Smith EE, Csapo I, Gurol ME, Brylka DA, et al. (2008) Spatial distribution of white-matter hyperintensities in Alzheimer disease, cerebral amyloid angiopathy, and healthy aging. Stroke 39: 1127–1133.
4. Firbank MJ, Lloyd AJ, Ferrier N, O'Brien JT (2004) A volumetric study of MRI signal hyperintensities in late-life depression. Am J Geriatr Psychiatry 12: 606–612.

5. Herrmann LL, Le Masurier M, Ebmeier KP (2008) White matter hyperintensities in late life depression: a systematic review. J Neurol Neurosurg Psychiatry 79: 619–624.

6. Barber R, Scheltens P, Gholkar A, Ballard C, McKeith I, et al. (1999) White matter lesions on magnetic resonance imaging in dementia with Lewy bodies, Alzheimer's disease, vascular dementia, and normal aging. J Neurol Neurosurg Psychiatry 67: 66–72.

7. Teodorczuk A, Firbank MJ, Pantoni L, Poggesi A, Erkinjuntti T, et al. (2010) Relationship between baseline white-matter changes and development of late-life depressive symptoms: 3-year results from the LADIS study. Psychol Med 40: 603–610.

8. Godin O, Dufouil C, Maillard P, Delcroix N, Mazoyer B, et al. (2008) White matter lesions as a predictor of depression in the elderly: the 3C-Dijon study. Biol Psychiatry 63: 663–669.

9. Soennesyn H, Oppedal K, Greve OJ, Fritze F, Auestad BH, et al. (2012) White matter hyperintensities and the course of depressive symptoms in elderly people with mild dementia. Dement Geriatr Cogn Dis Extra 2: 97–111.

10. Knopman DS, Penman AD, Catellier DJ, Coker LH, Shibata DK, et al. (2011) Vascular risk factors and longitudinal changes on brain MRI: the ARIC study. Neurology 76: 1879–1885.

11. Liao D, Cooper L, Cai J, Toole J, Bryan N, et al. (1997) The prevalence and severity of white matter lesions, their relationship with age, ethnicity, gender, and cardiovascular disease risk factors: the ARIC Study. Neuroepidemiology 16: 149–162.

12. Dufouil C, de Kersaint-Gilly A, Besancon V, Levy C, Auffray E, et al. (2001) Longitudinal study of blood pressure and white matter hyperintensities: the EVA MRI Cohort. Neurology 56: 921–926.

13. Hogh P, Garde E, Mortensen EL, Jorgensen OS, Krabbe K, et al. (2007) The apolipoprotein E epsilon4-allele and antihypertensive treatment are associated with increased risk of cerebral MRI white matter hyperintensities. Acta Neurol Scand 115: 248–253.

14. Appel J, Potter E, Bhatia N, Shen Q, Zhao W, et al. (2009) Association of white matter hyperintensity measurements on brain MR imaging with cognitive status, medial temporal atrophy, and cardiovascular risk factors. AJNR Am J Neuroradiol 30: 1870–1876.

15. Ballard C, O'Brien J, Barber B, Scheltens P, Shaw F, et al. (2000) Neurocardiovascular instability, hypotensive episodes, and MRI lesions in neurodegenerative dementia. Ann N Y Acad Sci 903: 442–445.

16. Thomas AJ, Perry R, Barber R, Kalaria RN, O'Brien JT (2002) Pathologies and pathological mechanisms for white matter hyperintensities in depression. Ann N Y Acad Sci 977: 333–339.

17. Kenny RA, Shaw FE, O'Brien JT, Scheltens PH, Kalaria R, et al. (2004) Carotid sinus syndrome is common in dementia with Lewy bodies and correlates with deep white matter lesions. J Neurol Neurosurg Psychiatry 75: 966–971.

18. Richardson J, Kerr SR, Shaw F, Kenny RA, O'Brien JT, et al. (2009) A study of orthostatic hypotension in late-life depression. Am J Geriatr Psychiatry 17: 996–999.

19. Colloby SJ, Vasudev A, O'Brien JT, Firbank MJ, Parry SW, et al. (2011) Relationship of orthostatic blood pressure to white matter hyperintensities and subcortical volumes in late-life depression. Br J Psychiatry 199: 404–410.

20. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology (1996) Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. Neurology 46: 1470.

21. Rutan GH, Hermanson B, Bild DE, Kittner SJ, LaBaw F, et al. (1992) Orthostatic hypotension in older adults. The Cardiovascular Health Study. CHS Collaborative Research Group. Hypertension 19: 508–519.

22. Andersson M, Hansson O, Minthon L, Ballard CG, Londos E (2008) The period of hypotension following orthostatic challenge is prolonged in dementia with Lewy bodies. Int J Geriatr Psychiatry 23: 192–198.

23. Sonnesyn H, Nilsen DW, Rongve A, Nore S, Ballard C, et al. (2009) High prevalence of orthostatic hypotension in mild dementia. Dement Geriatr Cogn Disord 28: 307–313.

24. Allan LM, Ballard CG, Rowan EN, Kenny RA (2009) Incidence and prediction of falls in dementia: a prospective study in older people. PLoS One 4: e5521.

25. Verwoert GC, Mattace-Raso FU, Hofman A, Heeringa J, Stricker BH, et al. (2008) Orthostatic hypotension and risk of cardiovascular disease in elderly people: the Rotterdam study. J Am Geriatr Soc 56: 1816–1820.

26. Raiha I, Tarvonen S, Kurki T, Rajala T, Sourander L (1993) Relationship between vascular factors and white matter low attenuation of the brain. Acta Neurol Scand 87: 286–289.

27. Allan LM, Ballard CG, Allen J, Murray A, Davidson AW, et al. (2007) Autonomic dysfunction in dementia. J Neurol Neurosurg Psychiatry 78: 671–677.

28. McKhann G, Drachman D, Folstein M, Katzman R, Price D, et al. (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34: 939–944.

29. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, et al. (2005) Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 65: 1863–1872.

30. Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, et al. (2007) Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 22: 1689–1707; quiz 1837.

31. Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, et al. (1993) Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 43: 250–260.

32. The Lund and Manchester Groups (1994) Clinical and neuropathological criteria for frontotemporal dementia. J Neurol Neurosurg Psychiatry 57: 416–418.

33. Aarsland D, Ballard CG, Halliday G (2004) Are Parkinson's disease with dementia and dementia with Lewy bodies the same entity? J Geriatr Psychiatry Neurol 17: 137–145.

34. Aarsland D, Rongve A, Nore SP, Skogseth R, Skulstad S, et al. (2008) Frequency and case identification of dementia with Lewy bodies using the revised consensus criteria. Dement Geriatr Cogn Disord 26: 445–452.

35. Conwell Y, Forbes NT, Cox C, Caine ED (1993) Validation of a measure of physical illness burden at autopsy: the Cumulative Illness Rating Scale. J Am Geriatr Soc 41: 38–41.

36. Oppedal K AD, Firbank MJ, Sonnesyn H, Tysnes OB, et al. (2012) White matter hyperintensities in mild Lewy body dementia. Dement Geriatr Cogn Dis Extra. In press.

37. Wakefield DB, Moscufo N, Guttmann CR, Kuchel GA, Kaplan RF, et al. (2010) White matter hyperintensities predict functional decline in voiding, mobility, and cognition in older adults. J Am Geriatr Soc 58: 275–281.

38. Scheltens P, Barkhof F, Leys D, Pruvo JP, Nauta JJ, et al. (1993) A semiquantative rating scale for the assessment of signal hyperintensities on magnetic resonance imaging. J Neurol Sci 114: 7–12.

39. Kapeller P, Barber R, Vermeulen RJ, Ader H, Scheltens P, et al. (2003) Visual rating of age-related white matter changes on magnetic resonance imaging: scale comparison, interrater agreement, and correlations with quantitative measurements. Stroke 34: 441–445.

40. Montgomery SA, Asberg M (1979) A new depression scale designed to be sensitive to change. Br J Psychiatry 134: 382–389.

41. Raz N, Yang Y, Dahle CL, Land S (2012) Volume of white matter hyperintensities in healthy adults: contribution of age, vascular risk factors, and inflammation-related genetic variants. Biochim Biophys Acta 1822: 361–369.

42. Schmidt R, Schmidt H, Fazekas F, Schumacher M, Niederkorn K, et al. (1997) Apolipoprotein E polymorphism and silent microangiopathy-related cerebral damage. Results of the Austrian Stroke Prevention Study. Stroke 28: 951–956.

43. Hirono N, Yasuda M, Tanimukai S, Kitagaki H, Mori E (2000) Effect of the apolipoprotein E epsilon4 allele on white matter hyperintensities in dementia. Stroke 31: 1263–1268.

44. Knopman DS, Penman AD, Catellier DJ, Coker LH, Shibata DK, et al. (2011) Vascular risk factors and longitudinal changes on brain MRI: the ARIC study. Neurology 76: 1879–1885.

45. Barber R, Gholkar A, Scheltens P, Ballard C, McKeith IG, et al. (1999) Apolipoprotein E epsilon4 allele, temporal lobe atrophy, and white matter lesions in late-life dementias. Arch Neurol 56: 961–965.

46. Hong YJ, Yoon B, Shim YS, Cho AH, Shin HE, et al. (2011) APOE epsilon4 allele status in korean dementia patients with severe white matter hyperintensities. J Alzheimers Dis 24: 519–524.

47. Crisby M, Bronge L, Wahlund LO (2010) Low levels of high density lipoprotein increase the severity of cerebral white matter changes: implications for prevention and treatment of cerebrovascular diseases. Curr Alzheimer Res 7: 534–539.

48. Bigler ED, Kerr B, Victoroff J, Tate DF, Breitner JC (2002) White matter lesions, quantitative magnetic resonance imaging, and dementia. Alzheimer Dis Assoc Disord 16: 161–170.

49. Hajjar I, Quach L, Yang F, Chaves PH, Newman AB, et al. (2011) Hypertension, white matter hyperintensities, and concurrent impairments in mobility, cognition, and mood: the Cardiovascular Health Study. Circulation 123: 858–865.

50. Cooke J, Carew S, O'Connor M, Costelloe A, Sheehy T, et al. (2009) Sitting and standing blood pressure measurements are not accurate for the diagnosis of orthostatic hypotension. QJM 102: 335–339.

51. Mehrabian S, Duron E, Labouree F, Rollot F, Bune A, et al. (2010) Relationship between orthostatic hypotension and cognitive impairment in the elderly. J Neurol Sci 299: 45–48.

52. Ha AD, Brown CH, York MK, Jankovic J (2011) The prevalence of symptomatic orthostatic hypotension in patients with Parkinson's disease and atypical parkinsonism. Parkinsonism Relat Disord 17: 625–628.

53. Passant U, Warkentin S, Gustafson L (1997) Orthostatic hypotension and low blood pressure in organic dementia: a study of prevalence and related clinical characteristics. Int J Geriatr Psychiatry 12: 395–403.

54. Scheltens P, Barkhof F, Leys D, Wolters EC, Ravid R, et al. (1995) Histopathologic correlates of white matter changes on MRI in Alzheimer's disease and normal aging. Neurology 45: 883–888.

55. Paternoster L, Chen W, Sudlow CL (2009) Genetic determinants of white matter hyperintensities on brain scans: a systematic assessment of 19 candidate gene polymorphisms in 46 studies in 19,000 subjects. Stroke 40: 2020–2026.

56. Vuorinen M, Solomon A, Rovio S, Nieminen L, Kareholt I, et al. (2011) Changes in vascular risk factors from midlife to late life and white matter lesions: a 20-year follow-up study. Dement Geriatr Cogn Disord 31: 119–125.

57. Debette S, Seshadri S, Beiser A, Au R, Himali JJ, et al. (2011) Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. Neurology 77: 461–468.