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Is there an association between orthostatic hypotension and cerebral white matter hyperintensities in older people? The Irish longitudinal study on ageing

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Abstract

Introduction: Orthostatic Hypotension (OH) is an abnormal drop in blood pressure (BP) that occurs following orthostatic challenge. OH is associated with increased risk of falls, cognitive impairment and death. White Matter Hyperintensities (WMH) on MR Brain are associated with vascular risk factors such as hypertension, diabetes and age. We examined whether extent White matter intensities were associated with presence of OH detected in a community dwelling population of older people.

Methods: Individuals from the MR sub-study of the Irish Longitudinal Study of Ageing underwent a 3 Tesla MR Brain scan to assess WMH severity (Schelten's Score). The scans were performed during the Wave 3 TILDA health assessment phase when the subjects also underwent assessment for OH with an active stand protocol. Data was analysed for association between WMH and vascular risks and orthostatic change in BP 10 second intervals during the OH evaluation.

Results: 440 subjects were investigated; median age 72 years (65–92 years) and 228 (51.5%) female. Range of Scheltens' Scores was 0–32. Mean score was 9.72 (SD 5.87). OH was detected in 68.4% (301). On linear regression, positive associations were found between Scheltens' Score and age, hypertension, prior history of stroke and TIA, and with OH at 30, 70, 90 and 100 seconds following standing ($p < 0.05$, O.R. 1.9–2.5).

Conclusion: WMD is associated with OH detected at multiple time points using active stand in community dwelling older subjects. Further research is necessary to evaluate the direction of this association.

Keywords

Orthostatic hypotension, white matter disease, population study, magnetic resonance imaging, blood pressure

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Introduction

White matter hyperintensities (WMH) as seen on MR Brain Scans have long been thought to reflect chronic small vessel cerebral ischaemia,[1] and are related to other cardiovascular risk factors including hypertension, advancing age and smoking.[2–6] Furthermore, there are established downstream associations between WMH and mortality,[7] cognitive decline, dementia,[8] and both silent and overt stroke.[9]

Blood pressure dysregulation in addition to elevated Blood Pressure (BP) has also been investigated with

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respect to WMH. The degree of hypotension in patients with hypersensitive carotid sinus responses correlates with density of deep white matter.[10] Orthostatic hypotension (OH) describes the blood pressure drop when an individual changes position (typically rising from lying or sitting to standing). Studies on subjects undergoing head-up tilt tests to identify OH have shown that subcortical infarcts and WMH are more common in individuals displaying OH and hypotension[11] and that OH is more common in subjects with sub-cortical infarcts.[12]

OH is a potent physiological stressor and it has been recently identified that OH, and in particular OH with delayed BP recovery, is a predictor of downstream brain health disorders in older adults such as depression, cognitive decline, gait and balance abnormalities manifesting as falls and syncope and even mortality.[12–15]

We hypothesised that increasing white matter disease may be associated with increased orthostatic BP variation and we therefore investigated the relationship between WMH, hypertension and characteristics of recovery of blood pressure following an orthostatic challenge in our population cohort.

Methods

Ethical approval for this study was obtained from the Trinity College Dublin School of Medicine Research Ethics Committee and participants provided written informed consent before the health assessment and again before MR scanning.

Design and participants

Subjects were identified from the Irish Longitudinal Study of Ageing (TILDA), a nationally-representative prospective cohort study of older Irish adults. Details of TILDA's design have been published previously[16]). Briefly, the study comprises a clustered stratified random sample of the community-dwelling population aged 50+ living in the Republic of Ireland. Fieldwork at Wave 1 (2009–2011) yielded a sample of 8175 non-demented adults aged 50 + (62% response rate). At Wave 1 and Wave 3 (2014), participants completed a computer assisted personal interview (CAPI) in their home (CAPI; N (Wave 3) = 6618; 85% response rate) which recorded demographics, health behaviours, comorbidities and medications. A majority also underwent a physical and cognitive health assessment with a trained research nurse at a health centre or at home (N = 5364; 82% response rate). A subset of Wave 3 health assessment participants who completed a health assessment including cardiovascular tests were later invited to complete the magnetic resonance imaging (MRI) protocol within 1 year of their health assessment.

TILDA magnetic resonance imaging subset

We recruited participants from the study population aged 65 and over, using a random sampling procedure of the main cohort to select eligible members of the health assessment sample. Research nurses informed participants of the MRI protocol following their health assessment and screened for common MRI contraindications. Participants provided voluntary informed consent before their scan appointment and consented for their scans to be provided to their GP in the event of an incidental finding.

In total, 578 participants participated in the TILDA MRI sub-study of whom T_{1w} datasets were acquired from 560 participants and 18 (3.1%) did not participate (due to claustrophobia/nerves [n = 14], or MRI contraindication [n = 4]). In this study we only utilised data from the 440 randomly selected subjects aged 65 years and older.

All brain imaging was performed on a 3 T MRI scanner (Achieva, Philips, Netherlands). T2 and Fluid-Attenuated Inversion Recovery (FLAIR) sequences were reviewed by two radiologists independently, with inter-observer correction. Diffusion Weighted Imaging (DWI) and Apparent Diffusion Coefficient (ADC) maps were analysed to identify acute parenchymal insults.

The primary objective of the study was to determine if an independent relationship existed between extent of White Matter Disease identified on these MR scans and indices of cardiovascular risk, including orthostatic hypotension.

Blood pressure measurements

Active stand tests of orthostatic blood pressure response were conducted on all subjects consistent with the European Society of Cardiology Guidelines current at the time of study[17] with the exception of duration of blood pressure evaluation.[16] During these tests, continuous phasic beat-to-beat blood pressure was measured non-invasively using digital photoplethysmography (Finometer® Midi) using standard protocols during 10 minutes supine rest in a quiet room followed by standing for 2 minutes. The Finometer has been validated for measurement of Blood Pressure by British Hypertension Society standards.[18] The 2 minute period post stand was to identify subjects who may suffer later recovery or later drops in Blood pressure. Orthostatic hypotension (OH) was defined as $\geq$20 mm Hg systolic blood pressure (SBP) (or $\geq$10 mm Hg diastolic blood pressure (DBP)) drop in from

baseline recordings during the 2 minutes post stand. The SBP and DBP at 10 second time-points post orthostatic challenge were compared with baseline values these timing were chosen to permit detection of both early and more delayed impaired orthostatic responses.

Other measures

Cardiovascular disease was collected as part of the TILDA questionnaire and defined as self-report of angina, congestive cardiac failure or prior myocardial infarction, while self-report was also elicited for a prior history of stroke, hyperlipidaemia and diabetes. Within TILDA antidepressant and cardiovascular medication use is classified with anatomical therapeutic classification codes and is used to help corroborate self reported disease. Blood Pressure readings were measured twice in seated position using Omron digital cuff by trained research nurse and mean of two values used for determination of hypertension.

Determination of extent of white matter disease

MR scans were evaluated and severity of WMH scored by radiologists trained in the analyses and blinded to the Orthostatic Blood Pressure results. Scheltens' semi-quantative visual rating scale was used to score subcortical hyperintensities.[19] These ill-defined hyperintensities are visible on both T2 and FLAIR sequences, and do not display cavitation. Scheltens' score was analysed with respect to OH at time intervals described, using the integrated statistical software package Stata (Statacorp). he Scheltens Scale is a visual rating scale that includes anchored, 7-point (0–6) severity ratings in periventricular (i.e., frontal horn, occipital horn, lateral bands), cortical (i.e., frontal lobe, temporal lobe, parietal lobe, occipital lobe), subcortical (i.e., caudate, putamen, globus pallidus, internal capsule, thalamus), and infratentorial (i.e., mesencephalon, pons, medulla, cerebellum) regions. Owing to the semi-quantative nature of the scale (i.e., non-equal spacing of unit-wise increments) and the skew apparent in the data, the Schelten's score variable was converted into an ordinal dependent measure (Score 0–19, 10–19, 20–29 and $\geq$30); this ordinal measure was analysed using ordered logistic regression. Covariates incorporated into the linear regression model were age sex, hypertension, prior stroke or TIA, hyperlipidaemia, diabetes, smoking, presence of cardiac murmurs and a combination of cardiovascular risk factors (atrial fibrillation, angina, prior myocardial infarction). The intention was to eliminate the potential confounding effect of such potential risk factors. A second model which integrated age and hypertension variables was also performed. A p-value of <0.05 was considered statistically significant.

Data Availability: TILDA provides anonymised publically accessible dataset files for reseach use. These files are hosted by the Irish Social Science Data Archive based in University College Dublin, and the Interuniversity Consortium for Political and Social Research (ICPSR) based in the University of Michigan. Researchers wishing to access the data must complete a request form, available on either the ISSDA or ICPSR website. Specific data from this substudy may also be provided by the authors on request.

Results

Median age of the 440 subjects was 72 years (65–92 years) at time of MR, and 228 (51.5%) were female. 270 (38.6%) of the cohort had a history of hypertension and 272 (38.2%) had hyperlipidaemia. Diabetes mellitus was present in 8.9% (39 individuals). Nine (2.0%) individuals reported a prior diagnosis of stroke or Transient Ischaemic Attack. Twenty-one (4.8%) individuals were active smokers and 181 (41.1%) were ex-smokers (Table 1). Prevalence of OH defined as above was 68.4% (301) at the subjects Wave 3 assessment. Prevalence of recovery in BP (a persistent drop of 20 mmHg in SBP or 10 mmHg in DBP) beyond 60 seconds was found in 56 individuals.

Scheltens' scoring of various brain regions demonstrated that the frontal and parietal lobes, and frontal caps were the most frequently identified foci of hyperintensities on T2 and FLAIR sequences (Table 2). The range of Scheltens' Scores was 0–32 out of a total achievable score of 84. Mean score of the cohort was 9.72 (SD 5.87). Coefficient of agreement for radiologists applying the score was strong (0.82)

Comparing Wave 3 data and Scheltens' Score, in and unadjusted model, positive associations were

Table 1. Population demographics (n = 440).

Variable	n (%)
Mean age at time of MRI, mean (range)	72 (65–92)
Female	228 (51.55)
Hypertension	270 (36.4)
Hyperlipidaemia	272 (38.2)
Diabetes	39 (8.9)
Prior stroke	3 (0.7)
Prior TIA	6 (1.4)
Active smoker	21 (4.8)
Ex-smoker	181 (41.1)
OH wave 1	327 (74.3)
OH wave 3	301 (68.4)

MRI: Magnetic Resonance Image; TIA: Transient Ischaemic attack; OH: Orthostatic Hypotension.

Table 2. Schelten's scores for individual brain regions.

Subcortical Hyperintensities	Mean (SD)
PV caps frontal	1.25 (0.51)
PV caps occipital	0.85 (0.65)
PV bands lateral ventricles	0.96 (0.52)
DWM frontal	2.47 (1.56)
DWM parietal	1.89 (1.71)
DWM occipital	0.15 (0.48)
DWM temporal	0.78 (1.16)
Caudate	0.01 (0.67)
Putamen	0.17 (0.67)
Globus pallidus	0.08 (0.44)
Thalamus	0.11 (0.45)
Internal capsule	0.33 (1.06)
Cerebellum	0.03 (0.21)
Midbrain	0.05 (0.30)
Pons	0.81 (1.26)
Medulla	0.00 (0.00)

Scheltens' score as applied to our cohort is represented above. "PV" refers to periventricular distribution of white matter hyperintensities, with a score of 6 achievable, depending on measurement. "DWM" refers to deep white matter hyperintensities, within the various cortical lobes, scored up to a maximum of 6 each, depending on measurements, number of lesions, and confluence. The basal ganglia, cerebellum and brainstem are scored in a similar fashion. Total score achievable is 84.

found between Scheltens' Score and age, hypertension, prior history of stroke and TIA, arrhythmia, presence of cardiac murmur and OH at a multiple timepoints (Table 3).

An ordered logistic regression was performed for this phase 3 data fitting terms for OH at each time point between 10 seconds and 110 seconds post stand, whilst adjusting for age, sex, smoking history, hypertension, hyperlipidaemia and diabetes (Table 4). This demonstrated a statistically significant association between WMH and OH remained at 4 points, 30, 70, 90 and 110 seconds (Table 4) following adjustment. This relationship was maintained at the same timepoints in a second model, where an integrated term for hypertension and age was used.

Discussion

This study demonstrates a relationship between WMH and OH detected at multiple time points from 30 seconds to 110 seconds in evaluations performed near the time of MRI in a randomly selected population of older, community dwelling adults.

This study is original in that it uses data from a longitudinal study of a very well characterized, randomly selected community dwelling sample of older adults, representative the over-65 of the population living in Ireland (14, 16,). The methodology used to identify Orthostatic Hypotension was robust, well-validated and met European Society of Cardiology Syncope Guidelines (,17) for conducting such assessments and the evaluations were conducted by experienced staff. The one inconsistency with the ESC guidelines was in duration of the observation period following stand. Most diagnostic Active Stand

Table 3. Unadjusted regression model with subcortical hyperintensity burden (Scheltens' score) as dependent variable; Wave 3 data.

	P value	Odds Ratio
Age at time of MRI	0.00	1.1
Sex (female)	0.543	1.121
Hypertension	0.010	1.67
Hyperlipidaemia	0.265	1.25
Diabetes	0.127	0.605
Angina	0.174	0.430
Prior heart attack	0.849	0.75
Prior stroke	0.020	8.25
Prior TIA	0.005	5.02
Cardiac murmur	0.798	1.14
Arrythmia	0.524	1.22
Atrial fibrillation	0.982	0.99
OH @ 10sec	0.273	0.76
OH @ 20sec	0.011	1.74
OH @ 30sec	0.004	2.09
OH @ 40sec	0.032	1.73
OH @ 50sec	0.009	1.98
OH @ 60sec	0.029	1.80
OH @ 70sec	0.001	2.69
OH @ 80sec	0.087	1.67
OH @ 90sec	0.022	2.03
OH @ 100sec	0.335	1.33
OH @ 110sec	0.005	2.3

MRI: Magnetic Resonance Image; TIA: Transient Ischaemic attack; OH: Orthostatic Hypotension.

Table 4. Integrated linear regression model of subcortical hyperintensity burden (incorporating potential confounding variables: age, sex, smoking history, hypertension, hyperlipidaemia and diabetes) and OH at sequential time intervals.

	P value	Odds Ratio
OH @ 10sec	0.832	0.95
OH @ 20sec	0.059	1.52
OH @ 30sec	0.018	1.87
OH @ 40sec	0.078	1.59
OH @ 50sec	0.079	1.62
OH @ 60sec	0.091	1.59
OH @ 70sec	0.002	2.50
OH @ 80sec	0.220	1.46
OH @ 90sec	0.015	2.15
OH @ 100sec	0.268	1.40
OH @ 110sec	0.003	2.48

guideline protocols now mandate a three minute stand;[17,20] however this has not been the practice of TILDA from outset.[16] Despite, the duration, we recorded a high incidence of OH and this is most likely due to the frequency of blood pressure measurements made on each subject.

Radiological techniques for conducting scans and identifying WMH were well validated. It is notable that an independent association between OH and WMH was detected at 70, 90 and 110 seconds and this may suggest that a more prolonged acive stand may have detected a stronger association if continued beyond 2 minutes.

Scheltens' semi-quantative scale was chosen to calculate extent of white matter disease because it is well validated,[20] commonly used and can be applied to routinely performed brain MRI. Our results were similar to those of other population studies (REF). It is possible that other more sophisticated measures of impairment of white matter integrity, such as diffusion tensor imaging (DTI) may show evidence of differing associations with OH but this was beyond the scope of this study.

As with most large population studies history of cardiovascular disese including angina, congestive cardiac failure, prior myocardial infarction, prior stroke and diabetes is self reported as part of the screening questionnaire and thus is not independently validated.

It is of note the prevalence of cardiovascular diseases and severity of white matter disease identified was somewhat less than in other patient studies. This is primarily because the study recruited specifically community dwelling older people rather than a specifically at-risk population as in previous research and is consistent with findings in other large population studies.[21,22] The sub-population of those undergoing MR scanning was representative of the study population.

White matter hyperintensities have been reported associated with dysfunction of a variety of physiological and cognitive processes. Visible damage to white matter pathways, combined with additional injury not evident on MR images may result in delayed compensatory responses to physiological challenges. The effect of a burden of white matter disease on cognition,[8] gait[23] and mood[24] is well characterized. WMH have also been reported associated with dysregulation of autonomically influenced physiological variables such as nocturnal heart rate[25] and respiration.[26] In this context it is perhaps unsurprising that WMH may impair rapid recovery from an orthostatic challenge given the reasonably complex neurophysiological process involved in achieving such recovery.

An increasing literature has characterized the clinical importance of OH. It is associated with an increased risk of, falls, and cognitive impairment and is associated with an increased risk of all cause death, cardiovascular disease and stroke.[27,28] Increasing recognition is being made of the importance of delayed recovery from OH rather than severity of BP drop encountered in mediating the pathological effect of OH. Our group has previously described a positive association between impaired OH BP recovery, falls that are injurious or unexplained,[15] and mortality. A question remains as to whether prolonged episodes of hypotension and consequent relative cerebral hypoperfusion may influence the progression of white matter disease and the development of further, larger or more confluent WMH. This study supports previous studies which have found some associations between OH and WMH. The Cardiovascular Health Study identified and association with OH detected using conventional sphygmomanometry in a study of 3301 people.[29] Another smaller study used the more sensitive plethsmographic continuous blood pressure monitoring in a small cohort of older subjects with depression and found an association with white matter disease. This is the largest study conducted to-date using plethysmography and confirms these findings.[30]

In identifying an association between OH and physical manifestations of brain injury represented by WMH, we feel we may have contributed to the understanding between OH, and cerebral white matter ischaemia. Further work is necessary to confirm the direction of association between OH and WMH and to assess which brain regions may in particular be associated with impaired BP recovery from Orthostatic Challenge.

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Contributorship

AB conducted the study and performed the analysis, DC helped with the analysis and performed statistical evaluation, JH proposed and designed the study, RAK conceived the TILDA and MR substudies and contributed to the design of the study, JM evaluated the scans with AB. All authors contributed to the writing of the paper.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval for this study was obtained from the Trinity College Dublin School of Medicine Research Ethics

Committee and participants provided written informed consent before the health assessment and again before MR scanning.

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Guarantor

Joseph Harbison is the guarantor and accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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