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White Matter Hyperintensities and Medication Adherence

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Abstract

White matter hyperintensities (WMH) are associated with hypertension, age, and cognitive function, but the association between WMH and medication adherence has not been examined. The intent of this investigation was to consider the potential implications of hypertension-related brain morphological changes on medication adherence and thereby improve understanding of the self-management consequences of hypertension. The associations between WMH, blood pressure, age, cognitive function (specifically assessments of prefrontal function), and medication adherence were examined in 16 middle-aged and older adults self-managing at least one prescribed antihypertensive agent. Magnetic resonance imaging using an axial fluid attenuated inversion recovery (FLAIR) sequence was used to assess the presence of WMH. Cognitive assessments included measures of executive function, working memory, attention, and immediate recall. Adherence was monitored for 8 weeks using electronic medication monitoring. More WMH were associated with poorer adherence ($r_s = -.25$) and with higher systolic blood pressure ($r_s = .46$), although these relationships were not statistically significant. WMH were associated with cognitive assessments in the expected direction including Digit Span Backward ($r_s = -.53$, $p < .05$). Adherence was associated with immediate memory ($r_s = .54$, $p < .05$) and inversely associated with failure to maintain set on the Wisconsin Card Sorting Test (WCST; $r_s = -.61$, $p < .05$). These findings provide preliminary evidence for the association between WMH, assessments of prefrontal function, and medication adherence.

Keywords

white matter hyperintensities (WMH); MRI; medication adherence; hypertension; cognitive; executive function

White matter hyperintensities (WMH) are high-intensity periventricular, or deep, patchy areas in the white matter of the brain viewed with magnetic resonance imaging (MRI) and are associated with neuronal loss, ischemic demyelination, and gliosis (Pantoni, 2002). Several factors are associated with the development of WMH including age (Basile et al., 2006), hypertension (Dufouil et al., 2001; van Swieten et al., 1991) and other diseases that affect the vascular system including diabetes (Murray et al., 2005). The associated factors may cause changes in brain morphology individually or may interact and thereby exacerbate

the effects of each other. For example, it has been suggested that hypertension exacerbates the brain morphological changes that accompany aging (Strassburger et al., 1997).

WMH are associated with cognitive decline (Breteler et al., 1994; De Groot et al., 2002; Deary, Leaper, Murray, Staff, & Whalley, 2003; Leaper et al., 2001). For example, individuals with WMH, particularly those with confluent lesions, demonstrate lower immediate and delayed recall and slower performance on Trail Making B and the Stroop interference tests (van Swieten et al., 1991). Perseveration on the Wisconsin Card Sorting Test is also linked to WMH in the frontal region (Gunning-Dixon & Raz, 2003; Raz, Rodrigue, & Acker, 2003). Cognitive function, particularly assessments of prefrontal function, has been shown to predict medication adherence among older adults (Insel, Morrow, Brewer, & Figueredo, 2006). If it is also shown that the presence of WMH predicts medication non-adherence, then further insights into the pathophysiology and morphology of WMH may provide crucial information for addressing medication adherence neurologically. Therefore, this investigation examined the associations among WMH, blood pressure, age, cognitive function, and medication adherence in middle-aged and older adults self-managing at least one prescribed daily antihypertensive agent. We hypothesized that the presence of WMH among older hypertensive adults would be associated with medication adherence.

Background

The pathologic origin of WMH is an area of some debate (Hoth et al., 2007; Pantoni, 2002; Wardlaw, Sandercock, Dennis, Starr, & Kalimo, 2003). Small-vessel disease has been implicated as a causal factor in the development of WMH. For example, intercellular adhesion molecule at baseline was associated with increasing severity of WMH 3 and 6 years later while controlling for age (Markus et al., 2005). There is increasing evidence that the origin of white matter lesions is related to endothelial factors (Hoth et al., 2007). Endothelial cell activation factors have been shown to be elevated in hypertension and may be the mechanism involved in the association between hypertension and WMH (de Leeuw, de Kleine, et al., 2002; Hjerkin, Seljeflot, Sandvik, Hjermann, & Arnesen, 2005; Komatsu et al., 1997; Nadar, Blann, & Lip, 2004). White matter changes may result from ischemic demyelination because of stenosis of small perforating arteries (Wardlaw et al., 2003). Others have suggested that WMH are a result of alterations to the blood–brain barrier with consequent tissue lesions from the edema fluid (Wardlaw et al., 2003).

Hypertension is associated with WMH (Dufouil et al., 2001), and WMH are associated with cognitive decline (Jokinen et al., 2005; Leaper et al., 2001). Cross-sectional and longitudinal evidence supports the association between hypertension and cognitive decline particularly when hypertension is untreated or undertreated (Elias, Wolf, D'Agostino, Cobb, & White, 1993; Swan et al., 1998; Waldstein, 1995). Although potential causal factors associated with the development of WMH have been sought, and the overall association of WMH and cognitive decline has been described, the functional implications associated with the presence of WMH are less well understood. An exception is work by Pantoni and colleagues (Inzitari, Carlucci, & Pantoni, 2000; Inzitari et al., 2007; Pantoni et al., 2005), who studied the functional effects of WMH in the elderly. Older adults who were either not impaired or

restricted in only one instrumental activity were classified as having mild, moderate, or severe age-related white matter changes (Inzitari et al., 2007). One year later, 9% of those in the mild, 16% of those in the moderate, and 24% of those in the severe classifications were limited on at least two instrumental activities of daily living.

Since WMH are inversely associated with cognitive function, the development of WMH should be inversely associated with medication adherence because it has been shown previously that cognitive assessments of prefrontal function were associated with medication adherence (Insel et al., 2006). In the current study, we sought to understand the relationships among the intensity and size of WMH, blood pressure (systolic and diastolic), age, cognitive function (executive function, working memory, and immediate verbal memory), and medication adherence among 16 adults over 50 years of age, all self-managing at least one antihypertensive agent. Identifying the relationship between WMH and medication adherence is critical to understanding the neural mechanisms associated with medical nonadherence. Such an understanding could subsequently facilitate targeted treatment in a challenging subgroup of the chronically ill.

Methods

This study was a descriptive exploratory study examining the associations among the variables of interest: WMH, blood pressure, age, cognitive function, and medication adherence.

Participants

Participants—16 middle-aged and older adults taking at least one prescribed daily medication for hypertension—were recruited at community centers in a southwestern city in the United States. To obtain a broad sample, community centers serving both low-income and higher income residents were included. Cognitive function is known to be associated with education, and education can vary systematically between high-income and low-income neighborhoods (Ainsworth, 2002; Leventhal & Brooks-Gunn, 2003). Potential participants were told that the purpose of the study was to examine the relationships among how individuals take daily prescribed medications, blood pressure, thinking and remembering ability, and brain structures. Individuals eligible to participate were 50 years of age or older, able to speak and read English, and taking at least one prescribed medication for hypertension that they were willing to place in a monitored medication container. Potential participants were excluded if they had a history of neurological disorder or serious head injury, were pregnant or had a metal or mechanically activated implant that would prevent them from being in an MRI scanner. Participants were also screened for claustrophobia or anxiety or other problems that would prevent them from being in a scanner.

Assessments

General demographic information including age, gender, educational level, self-rated health status, and the length of time since receiving a diagnosis of hypertension were obtained through interview using a demographic questionnaire designed for this study.

The Mini Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975) and the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977) were used to indicate the presence of symptoms of dementia and depression, respectively. The MMSE and CES-D are considered valid and reliable screening instruments for dementia and depression and are widely used (Spree & Strauss, 1998).

Adherence to an antihypertensive medication was monitored for 8 weeks using an electronic medication monitoring cap (Medication Electronic Monitoring System, MEMS) manufactured by Aardex. This medication monitoring system records the time and date the medication container is opened. The data from the cap are communicated to a software program that provides adherence information in both number and percentage for overall prescribed doses, daily adherence, and adherence to a schedule. For this investigation, the percentage of daily doses taken as prescribed was used as the adherence measure. In this way, errors of omission (not opening the medication container to take a dose each day) and errors of commission (opening the medication container too many times) were recorded as errors. Measures of overall adherence using number or percentages would not capture errors of omission or commission because opening the bottle twice one day and none the next day would indicate no errors though errors existed.

A seated blood pressure measure was taken with a digital blood pressure monitoring device (Omron HEM 739, Omron Healthcare, Inc. Bannockburn, IL) at the time of initial data collection to obtain systolic and diastolic blood pressure data.

The battery of cognitive measures included subscales from the Wechsler Memory Scale—Third Edition (WMS-III; Wechsler, 1997). Immediate memory was assessed using the total immediate recall score from the Logical Memory subtest, working memory was assessed using the Digit Span Backward and Letter-Number Sequencing subtests, and attention was assessed using the Mental Control subtest. Executive function was assessed with the Executive Exit Interview (EXIT 25; Royall, Mahurin, & Gray, 1992) and the 64-card computer version of the Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Kay, & Curtis, 1993). The WCST provides indices on problem-solving behavior including the number of categories achieved in card sorting, failure to maintain set once a category is recognized, and the number of perseveration errors. Perseveration errors are errors that are made as the individual continues to use a sorting rule that is no longer effective. Validity of the 64-card version of the WCST and comparability to the standard 128-card version have been extensively demonstrated (Greve, 2001). Studies report a consistent three-factor structure across different populations. Stability of the WCST suggests individuals improve on the second testing; however, none of the participants were tested twice on this measure. The EXIT 25 is a “bedside measure” of executive function and is composed of 25 items. Examples of items are verbal fluency in 1 min with the letter A and recognizing the color of a word rather than naming the word. Higher scores are indicative of greater impairment. Mental control as measured by the WMS-III involves simple and complex auditory attention (Lezak, Howieson, & Loring, 2004).

Within a week following initial data collection and during the time adherence was monitored, participants completed an MRI scan on a GE Signa 1.5 Tesla scanner that

included an axial fluid attenuated inversion recovery (FLAIR) sequence. FLAIR is the preferred method for obtaining information on WMH (Murray et al., 2005). The FLAIR sequence collection consisted of 24 slices with the following parameters: TE = 120; TR = 9000; TI = 2200; slice thickness = 5.0 mm; skip = 1.0 mm; FOV = 22 cm²; matrix = 256 × 192. WMH on FLAIR images were scored using a procedure modified from Rezek and colleagues (Rezek, Morris, Fulling, & Gado, 1987). In this procedure, 42 standard locations, including left, right, anterior, posterior, subcortical, and periventricular areas across six slices, were examined and scored by two raters. A WMH score on a 0–6-point scale was given for each location based on the size of lesions (<1 cm², 1 cm², or >1 cm²) and degree of lucency (mild or severe) within that region. For example, a mild 0.5 cm² lesion was rated 1, a mild 2 cm² lesion was rated 3, and a severe 1 cm² lesion was rated 5. The 42 scores were then summed to provide a total WMH score for each participant, with scores potentially ranging from 0 to 192. Interrater reliability for this measure was .96.

Procedure

Approval to conduct this investigation was obtained from the Institutional Review Board, Human Subjects Protection Committee. Initial data collection occurred either at the university or in a private room of a community center, whichever was easier and more comfortable for the participant. Initial data collection took less than 3 hr with a formal consent procedure. Baseline data included the demographic and depression questionnaires, cognitive assessments and blood pressure. At this time participants also transferred one prescribed medication to the medication monitoring container. When participants were taking more than one medication to control high blood pressure, participants were asked which medication was specifically for their blood pressure. The following algorithm was used: If the participant was taking an ace inhibitor, it was chosen first, then the beta blocker, calcium channel blocker, and finally, the less specific diuretic. Participants were then scheduled for an appointment at the university for an MRI scan. The same MRI scanner was used for all participants. Scanning took less than 1 hr. Study personnel visited participants in their homes or at a community center 8 weeks later to obtain the monitoring cap. Participants were given \$50 in appreciation of their time.

Results

Demographic information is reported in Table 1. There were 9 male and 7 female participants, most of whom were at least high school graduates. Of the 16 participants, 13 were White (81%), 1 was Mexican American (6%), and 2 were African American (12%). Although the majority reported having had high blood pressure for 1 to 5 years, 1 individual indicated a 30-year history of hypertension. Symptoms of depression were prevalent in half of this sample, with 8 of the participants scoring above the CES-D cutoff score of 16 for depression (McDowell & Newell, 1996). The majority of participants ($n = 14$) were prescribed a once-a-day antihypertensive agent, with the remaining 2 prescribed the monitored medication twice a day.

This study was exploratory, and we used .05 as the p value to indicate statistical significance; however, we recognize that with the number of correlations that were

examined, this is lenient. The associations of adherence, cognitive measures, and WMH are reported in Table 2 with correlations based on Spearman rank order because of the small sample size. The association between WMH and adherence ($r_s = -.25$) was not statistically significant. Although the associations between WMH and systolic blood pressure of $r_s = .46$ and between WMH and age of $r_s = .30$ were in the expected direction, they were not statistically significant in this study. The only statistically significant association between WMH and a cognitive measure was that of Digit Span Backward ($r_s = -.53, p < .05$).

Medication adherence was significantly associated with immediate memory ($r_s = .54, p < .05$) and inversely associated with failure to maintain set on the WCST ($r_s = -.61, p < .05$). Adherence was also inversely associated with depression symptoms ($r_s = -.52, p < .05$).

Discussion

Others have shown that WMH are associated with age and hypertension; however, there is sparse information in the literature about the real life implications of white matter changes among middle-aged and older adults self-managing a chronic illness, in this case hypertension. Although the small sample size in the current study limits our ability to reach strong conclusions, we did find some significant relationships. In this discussion, we will examine the size of the correlation coefficient to suggest the relative value of the identified associations and a viable direction for future research geared toward improving understanding of self-management in this population. Correlational measures are used as an indication of effect size as suggested by Cohen and colleagues (1983, 2003) and Grissom and Kim (2005).

WMH were associated with age and systolic blood pressure in the expected direction. Although not statistically significant, this finding is consistent with the literature indicating that severity of hypertension is associated with WMH, particularly when hypertension is poorly controlled (de Leeuw, de Groot et al., 2002; Soderlund, Nyberg, Adolfsson, Nilsson, & Launer, 2003). Among individuals with hypertension, WMH increases as age increases and hypertension is poorly controlled (Dufouil et al., 2001).

WMH were also associated with Digit Span Backward, a task that involves working memory in that digits must be retained in memory and then recalled backward. These data support work indicating that cognitive tasks that involve working memory are associated with WMH.

Adherence was significantly associated with immediate recall (from Logical Memory) and Failure to Maintain Set (from the WCST). These findings, combined with findings from earlier work, suggest that immediate memory and attention are important to understanding medication adherence among older community-dwelling adults (Insel et al., 2006).

WMH have been associated with global or selective cognitive deficits, depression, and motor and gait impairment among the elderly individuals and hence have been used as an indicator of increasing disability in this population (Inzitari et al., 2000, 2007; Pantoni et al., 2005). Similar to this, we found a significant negative association between adherence and symptoms of depression. Given that symptoms of depression may be particularly prevalent

in this population, mood symptoms need to be further evaluated as a possible mitigating factor in the link between neurological/cognitive function and adherence.

WMH may mediate the association between blood pressure and cognitive function (Raz et al., 2003). A benefit of this investigation was the opportunity to look at the associations between WMH, age, cognitive measures, and an everyday functional activity of adhering to prescribed medications. Although sample size limits our ability to examine the role of WMH as a mediator between blood pressure and cognition and then cognitive function as a mediator between WMH and medication adherence, continuing work in this field could help test these hypothesized relationships.

Attention to the everyday consequences of high blood pressure and associated structural brain changes has the potential to reinforce preventive strategies to enhance optimal brain health. Finding associations among brain changes, cognitive function and everyday functional outcomes such as managing medications should alert clinicians to the possible increased difficulties individuals with hypertension may have self-managing a medication regimen.

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Table 1
Mean, Standard Error, and Range for Demographic and Relevant Variables

Variable	Mean (SE)	Range
Age (years)	70.19 (1.78)	53–87
Education (years)	13.13 (0.65)	8–16
Mini Mental State Exam (MMSE) score	27.63 (.63)	23–30
Depression (CES-D) score	20.13 (2.29)	9–44
Systolic blood pressure	146.33 (5.86)	118–186
Diastolic blood pressure	80 (4.29)	58–110
Medication adherence ^a (%)	67.86 (7.26)	7.1–100
White matter hyperintensities score	44.56 (6.18)	16–112

NOTE: CES-D = Center for Epidemiologic Studies Depression Scale.

^aMedication adherence = percent of daily doses taken as prescribed.

Spearman Rank Order Correlations of Adherence, the Cognitive Measures, and White Matter Hyperintensities (WMH)**Table 2**

Variables	Adherence	MMSE	CES-D	Log Mem	Let Num	Men Cont	Digit Back	WCST CC	WCST per	WCST fm	EXIT25
MMSE	.31										
CES-D	-.52*	-.06									
Log Mem	.54*	.39	.07								
Let Num	.30	.17	-.24	.03							
Men Cont	.12	.70**	.30	.33	.14						
Digit Back	.41	.34	.10	.32	.39	.51*					
WCST CC	.19	.36	-.40	.19	.41	.09	.21				
WCST per	-.13	-.33	.37	.08	-.04	-.14	.17	-.74**			
WCST fm	-.61*	-.12	-.08	-.43	-.39	-.27	-.48	.09	-.34		
EXIT25	-.45	-.44	.33	-.30	-.29	-.49	-.41	-.16	.06	.02	
WMH	-.25	-.23	-.23	.01	-.08	-.46	-.53*	.25	-.28	.43	.23

NOTES: CES-D = Center for Epidemiologic Studies Depression Scale; Digit Back = Wechsler Memory Scale-Third Edition (WMS-III), Digit Span Backward; EXIT25 = Executive Exit Interview; Let Num = WMS III Scaled Score Letter Number Sequence; Log Mem = WMS-III Scaled Score Logical Memory Recall; MMSE = Mini Mental State Exam; Men Cont = WMS-III Mental Control; WCST CC = Wisconsin Card Sorting Test Categories Completed; WCST per = Wisconsin Card Sorting Test perseveration standard score; WCST fm = Wisconsin Card Sorting Test Failure to Maintain Set; WMH = White Matter Hyperintensities.

* $p < .05$.

** $p < .01$.