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Original Research Article

Cognitive Impact of Lacunar Infarcts and White Matter Hyperintensity Volume

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Key Words

Cognition · Memory · Montreal Cognitive Assessment · Lacune · White matter hyperintensity · Magnetic resonance imaging

Abstract

Background: Subcortical lacunar infarcts and white matter hyperintensities (WMH) are common neuroradiological findings, but few studies associate between these insults and cognition in a community-dwelling population. ***Methods:*** The Dallas Heart Study is a population-based initiative whose assessments included demographic and clinical findings including brain MRI and the Montreal Cognitive Assessment (MoCA). The presence and number of lacunes in subjects aged over 55 years were assessed by study physicians. The WMH volume was measured by an automated method. The association between the presence and number of lacunar infarcts and of WMH volume with the total MoCA score and subdomains was assessed using linear regression with adjustment for age, gender and self-reported ethnicity. ***Results:*** In 609 subjects with valid data, both the presence and the increasing number of lacunes were associated with lower MoCA scores, even after adjusting for demographic variables. The presence of lacunes was also associated with lower scores in the memory, executive and attention subdomains. The WMH volume was not significantly associated with the MoCA score. ***Conclusion:*** The presence and increasing number of lacunes in midlife is associated with a lower performance in multiple domains of a cognitive screening measure after adjusting for demographic factors.

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Introduction

Cerebrovascular disease and insults are risk factors for the cognitive decline of various etiologies [1–3]. Two commonly accepted manifestations of cerebrovascular disease, subcortical lacunar infarcts and white matter hyperintensities (WMH), are common findings in older adults [4, 5]. Cerebral microvascular disease lowers the threshold for cognitive impairment and dementia [6], but relatively little is known about its association with cognitive deficits in younger, midlife samples, particularly among multiethnic subjects [7].

Vascular risk factors for cognitive decline include hypertension, hypercholesterolemia, diabetes, heart disease and smoking. The risk for developing Alzheimer's disease has been shown to increase with the number of vascular risk factors present [3, 8], and the presence of diabetes has been particularly contributory [9–11]. Among these risk factors, hypertension has been shown to result in the greatest attributable risk for all-cause dementia [6]. Reducing high blood pressure has been suggested as a protection against the development of cognitive decline [12, 13]. Two imaging markers indicating vascular insult to the brain, particularly from hypertension, are lacunar infarction and WMH volume.

Existing studies of the cognitive impact of these findings of chronic cerebrovascular diseases were mostly performed in older, homogenous populations, and there is a paucity of study in younger, community-dwelling subjects. Elderly patients have shown decreased psychomotor speed and global cognitive function with an increasing volume of white matter lesions [14]. The Framingham Offspring Study also showed an association between WMH and lower performance on specific cognitive tests in a large, mostly white sample of mean age 61 years. Similarly, the finding of incident silent brain infarcts after a mean 3.6-year observation of elderly patients showed worse performances on cognitive testing [15]. In the settings of acute lacunar infarcts, an increased WMH burden has been associated with some tests of executive dysfunction, while other general cognitive tests such as the Chinese version of the Mini-Mental State Examination were not significantly related [16]. The Leukoaraiosis and Disability Study (LADIS) also found, in an older European sample, that after adjusting for WMH burden, the presence of lacunar infarction independently correlated with measures of cognitive impairment [17].

The Northern Manhattan Study [7] added important information about the associations of lacunes and WMH with psychomotor speed and cognitive flexibility in a relatively younger multiethnic sample. They evaluated 656 individuals (61% Hispanic, 21% Black and 18% White, mean age 70.4 years) and found that the WMH volume was associated with a grooved pegboard ($p = 0.004$) and color trails 2 ($p = 0.016$), but not color trails 1 ($p = 0.135$). Lacunar infarctions were associated with color trails 2 in the frontal region ($p = 0.022$). The Chicago Health and Aging project evaluated 575 participants in a slightly older biracial sample (58% Black, 42% White, mean age 79.8 years) [18]. They evaluated 17 cognitive tests grouped into 5 divisions: episodic memory, semantic memory, working memory, perceptual speed and visuospatial ability. Surprisingly, the presence of lacunar infarctions in this group was weakly associated with a slightly higher score on the test of general cognitive function ($p = 0.047$). Lacunes did not correlate with any of the domains when evaluated individually. The WMH volume did correlate with a lower score on the global test of general cognitive function ($p < 0.001$) and with all the domains evaluated individually. The lack of an association with a lower cognitive performance for lacunes in this sample, however, limits our ability to interpret the relative contribution of these findings. The Atherosclerosis Risk in Communities (ARIC) Study evaluated 1538 individuals (mean age 62.5 years, 51% Black) [19]. They found that visual grading of WMH severity correlated with cognitive function but that this was attenuated and no longer retained significance after adjusting for the presence of lacunar infarcts.

Our aim was to ascertain if the presence of 2 MRI markers of microvascular disease related to vascular risk factors, lacunar infarcts and WMH volume have a detectable impact on cognition assessed in a multiethnic sample with considerable variability in education and economic status. The instrument used here was the Montreal Cognitive Assessment (MoCA) [20], a measure of global cognitive function becoming more widely used in office screening for dementias. The MoCA is a 30-point scale that assesses a wide range of cognitive abilities including memory, visuospatial function, executive function, attention, language and orientation.

Materials and Methods

The Dallas Heart Study (DHS) is a population-based investigation employing biochemical, imaging and anatomic measures to study the development of cardiovascular disease [21]. Each subject gave written consent to participate in the study under a protocol approved by the UT Southwestern Institutional Review Board. Data collected included demographic information, medical history, physical examination, multiple laboratory measures as well as MRI of the brain and MoCA.

The subjects selected were persons aged 55 years and older who had a valid MoCA score and a brain MRI available. This age is the cutoff used for subjects eligible for the study at the UT Southwestern Alzheimer's Disease Center. Age, gender, race and education were also recorded.

2-D axial FLAIR images were acquired on a 3-tesla MRI system (Achieva, Philips Medical Systems). Thirty-two slices were acquired with TR/TE/TI = 11,000/130/2,800 ms, ETL = 44, SENSE factor = 2, FOV = 250 × 250 mm, 4-mm slice thickness with a 1-mm gap between slices and matrix of 240 × 138 yielding a voxel size of 4 × 0.96 × 1.33 mm = 5.11 mm [22]. Lacunar infarcts were detected and counted by a study physician (M.W.W.) and confirmed by a neuroradiologist (K.S.K.). Lacunes were reported as 'absent' or 'present'. Those with lacunes present were then subcategorized as having 1, 2 or ≥3 lacunes. The WMH volume was measured by an automated quantification algorithm using the FMRIB Software Library (FSL) [23, 24], was log transformed to achieve normal distribution and is expressed as percentage of brain volume [25].

MoCA testing was conducted by a trained staff. Cognition was measured by the total MoCA score and several subdomains. *Memory* was tested with a free recall of 5 words, *visuospatial* function with clock drawing and complex figure copying tasks, *executive function* with trail making, phonemic fluency and verbal abstraction, *attention* with targeted tapping, serial subtraction and digit spans forward and backward, *language* with confrontation naming, repetition and phonemic fluency and *orientation* was to place and time.

Total MoCA and the subdomains of memory, visuospatial function, executive function, attention, language and orientation were tested as continuous variables for the interaction with the presence or absence of lacunes. Additionally, the total MoCA score was tested against the number of lacunes and log volume of WMH by multiple linear regressions. Demographics including age, gender, race and education were controlled for each analysis. Education was defined as either high school completion or less.

Results

There were 609 subjects with valid demographic, cognitive testing and imaging data. Table 1 presents the baseline characteristics of the selected study participants. The sample included 61.5% females and 45.5% Black. Five subjects reported no formal education (recorded as '0'), and 27 reported less than 6 years of education. MoCA scores ranged from 9

Table 1. Baseline characteristics of DHS subjects with 3-tesla brain MRIs

Variable	n	Min.	Max.	Mean	SD
Age, years	738	55	85	61.75	4.92
Lacunes, n	715	0	≥3	0.11	0.44
WMH, ml	715	0.08	83	2.68	5.36
Education, years	728	0	16	12.90	2.27
MoCA score, points	609	9	30	22.99	4.00
Subjects, n (%)	735				
Female	452 (61.5)				
Male	283 (38.5)				
Lacunes, n (%)	735				
Absent	666 (93.3)				
Present	48 (6.7)				

Table 2. MoCA score and subdomains as predicted by lacunes and WMH

Domain	Lacune presence		Lacune count		WMH volume	
	Beta	Pr>t	Beta	Pr>t	Beta	Pr>t
Total score	–1.830	<0.01	–1.032	<0.01	0.030	0.84
Memory	–0.537	0.03				
Visuospatial	–0.086	0.59				
Executive	–0.623	<0.01				
Attention	–0.694	<0.01				
Language	–0.485	0.10				
Orientation	–0.082	0.15				

to 30 points. Lacunes were detected in 6.7% (n = 48) of MRIs. A single lacune was counted in 34 subjects, while 2 were found in 13 subjects and there were 8 subjects with ≥3.

Table 2 presents the test of the continuous variables for the total MoCA score and each subdomain of cognitive function against the presence of lacunes, adjusted for age, gender, race and education. The presence of lacunes remained a significant predictor of the total MoCA score even after adjusting for demographic data. Additionally, it was predictive of scores in the subdomains of memory, executive function and attention, but not for visuospatial function, language or orientation. Additionally presented is the test of the continuous variables for the total MoCA score against the number of lacunes as a continuous variable and also the log WMH volume. The number of lacunes was selected as a significant predictive of the total MoCA score after adjusting for demographic factors. The log WMH volume was not a significant predictor.

Discussion

This large, community-based study shows that both the presence and number of lacunar infarcts are associated with lower cognitive function, even after correction for age, gender, race and education. The predictive value held true for the subdomains of memory, executive function and attention, suggesting a possible differential effect of higher impact of lacunes in hippocampal or cortical domains; however, it was not predictive of visuospatial function. Language functions appeared to be unaffected. On the other hand, there was not the expected relationship between WMH volume and MoCA scores. The latter finding suggests that, in our

nonclinical relatively younger population, there is no impact on cross-sectional difference in MoCA score of presumably ischemic changes in the absence of frank brain infarction. In clinical investigations, impaired cognitive scores should not be correlated with the presence of WMH alone, without the adjustment for a presence of lacunar infarction.

There are several limitations to this study. Its cross-sectional methodology limited the ability to determine if the presence of cerebrovascular insult predates any change in cognitive performance. The relatively young mean age prevents further analyses in older cohorts in which cognitive disorders are more prevalent. Additionally, the MoCA was not developed in a multiethnic diverse population, possibly affecting its utility here.

In conclusion, in this large, community-based study, the presence of lacunes in a middle-aged and aging population is associated with lower measures of cognition in multiple domains after adjusting for demographic factors. An increasing volume of WMH was not significantly associated with decreased measures of cognition.

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