Age-associated leukoaraiosis and cortical cholinergic deafferentation

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ABSTRACT

Objective: To investigate the relationship between age-associated MRI leukoaraiosis or white matter hyperintensities (WMH) and cortical acetylcholinesterase (AChE) activity.

Background: One possible mechanism of cognitive decline in elderly individuals with leukoaraiosis is disruption of cholinergic fibers by strategically located white matter lesions. Periventricular lesions may have a higher chance of disrupting cholinergic projections compared with more superficial nonperiventricular white matter lesions because of anatomic proximity to the major cholinergic axonal projection bundles that originate from the basal forebrain.

Methods: Community-dwelling, middle-aged and elderly subjects without dementia (mean age 71.0 ± 9.2 years; 55–84 years; $n = 18$) underwent brain MRI and AChE PET imaging. The severity of periventricular and nonperiventricular WMH on fluid-attenuated inversion recovery MRI images was scored using the semiquantitative rating scale of Scheltens et al. [^{11}C]methyl-4-piperidiny propionate AChE PET imaging was used to assess cortical AChE activity. Age-corrected Spearman partial rank correlation coefficients were calculated.

Results: The severity of periventricular ($R = -0.52$, $p = 0.04$) but not nonperiventricular ($R = -0.20$, not significant) WMH was inversely related to global cortical AChE activity. Regional cortical cholinergic effects of periventricular WMH were most significant for the occipital lobe ($R = -0.58$, $p = 0.02$).

Conclusions: The presence of periventricular but not nonperiventricular white matter hyperintensities (WMH) is significantly associated with lower cortical cholinergic activity. These findings support a regionally specific disruption of cholinergic projection fibers by WMH. *Neurology*® 2009;72:1411–1416

GLOSSARY

AChE = acetylcholinesterase; **AD** = Alzheimer disease; **CADASIL** = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; **CPT-RT** = Conners continuous performance test reaction time; **CPT-SE** = Conners continuous performance test standard error; **FLAIR** = fluid-attenuated inversion recovery; **FWHM** = full-width at half-maximum; **MMSE** = Mini-Mental State Examination; **nbM** = nucleus basalis of Meynert; **NEX** = number of excitations; **NS** = not significant; **[^{11}C]PMP** = [^{11}C]methyl-4-piperidiny propionate; **SPGR** = spoiled gradient recall; **TAC** = time-radioactivity curve; **TE** = echo time; **TMT-BA** = Trail Making Test B minus A; **TR** = repetition time; **VOI** = volume of interest; **WMH** = white matter hyperintensities.

White matter lesions of aging are commonly seen on brain MRI studies often in the context of cardiovascular disease and may be associated with cognitive abnormalities.^{1,2} One possible mechanism of cognitive decline in individuals with leukoaraiosis is disruption of cholinergic fibers by strategically located white matter hyperintensities (WMH). The cholinergic neurons of the nucleus basalis of Meynert (nbM) provide the principal cholinergic input of the cerebral cortex.³ These cholinergic axons are mostly unmyelinated⁴ and may be more vulnerable to aging or disease-related changes in the white matter. For example, a postmortem study in a patient with cerebral autosomal dominant arteriopathy with subcortical infarcts and leu-

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koencephalopathy (CADASIL) provides anatomic evidence that cortical cholinergic projections from the nbM can be affected by white matter lesions in the absence of Alzheimer disease (AD).⁵

The cholinergic trajectories of white matter pathways linking the nbM with the cerebral cortex have been traced immunohistochemically in the human brain.⁴ These cholinergic pathways arise from the deep forebrain looping closely around the anterior corpus callosum and the frontal horns of the ventricles. The lateral pathway passes lateral to the ventricles through the external capsule before fanning out to innervate the cerebral cortex. The medial pathway passes through the white matter deep to the cingulate gyrus.⁴ The anatomic location of the cholinergic projection axons suggest that more deeply located, periventricular lesions may have a higher probability of disrupting these fibers compared with more superficial or subcortical WMH.

To our knowledge, the relationship between WMH and cortical cholinergic activity in normal aging has not been studied in vivo. The objective of this study was to investigate the relationship between periventricular and nonperiventricular WMH and in vivo cortical acetylcholinesterase (AChE) in community-dwelling, middle-aged and elderly subjects without dementia using MRI and PET neuroimaging techniques. We used [¹¹C]methyl-4-piperidinyl propionate ([¹¹C]PMP) PET imaging to assess cortical AChE activity. We hypothesized that increased severity of periventricular WMH is associated with lower levels of cortical AChE activity.

METHODS Subjects. Community-dwelling, middle-aged and elderly subjects without dementia ($n = 18$; 11 women, 7 men) were recruited from a larger study of community-dwelling subjects on mobility functions and aging.⁶ Subjects eligible for participation in the current study had no evidence of cortical strokes on MRI but had variable presence of leukoaraiosis (age requirement 55 years or older), had normal neurologic examination results, and were willing to undergo the AChE PET imaging procedure. None of the subjects were taking cholinergic or anticholinergic drugs. Clinical data from a selected psychomotor, information processing and executive function test battery included the Conners continuous performance test reaction time (CPT-RT) with standard error (CPT-SE),⁷ the Trail Making Test B minus A (TMT-BA),⁸ and the grooved pegboard test (Lafayette Instruments, Lafayette, IN). The study was approved by the institutional review boards of both the University of Pittsburgh and the Veterans Affairs Medical Center. Informed con-

sent was obtained from all subjects after the study's procedures were fully explained.

Magnetic resonance methods. All subjects underwent brain MRI using a Signa 1.5-tesla scanner (GE Medical Systems, Milwaukee, WI) with a standard head coil. Volumetric spoiled gradient recall (SPGR) sequences (echo time [TE] = 5, repetition time [TR] = 25, flip angle = 40 degrees, number of excitations [NEX] = 1, slice thickness = 1.5 mm) and fast fluid-attenuated inversion recovery (FLAIR) (TR/TE = 9,002/56 msec effectively, inversion time = 2,200 msec, NEX = 1, slice thickness = 5 mm) were obtained. Axial sequences were obtained with a 24-cm field of view and a 192×256 -pixel matrix. No contrast was administered. The presence of white matter signal hyperintensities on the FLAIR images was scored by one investigator (N.I.B.) who was blind to the clinical and PET data using the semiquantitative rating scale by Scheltens et al.⁹ This scale has significant correlation with quantitative volumetric measurements of white matter changes.¹⁰ The scale of Scheltens et al. provides ratings of subcortical signal hyperintensities according to size and number of lesions including periventricular and nonperiventricular WMH. Periventricular hyperintensities (frontal, occipital, and lateral aspects) have a total bilateral score of 0 to 12, with a subgroup score of 0 to 2 (0 = no abnormalities, 1 = hyperintensity ≤ 5 mm, 2 = hyperintensity > 5 mm and < 10 mm; hyperintensities > 10 mm are considered part of nonperiventricular hyperintensities); nonperiventricular hyperintensities are scored for each lobe following size criteria per lesion and total number of lesions (total score 0–24 per lobe).⁹ We also used the cholinergic pathways hyperintensities scale developed by Bocsi et al.¹¹ This scale provides regionally weighted scores depending on presence of WMH in anatomic landmarks in proximity of the cholinergic pathways.

AChE PET imaging. The [¹¹C]PMP radioligand is an acetylcholine analog that serves as a selective substrate for AChE hydrolysis.¹² The hydrolyzed radioligand becomes trapped as a hydrophilic product locally in the brain following the AChE biodistribution. AChE has been recognized since 1966 as a reliable marker for brain cholinergic pathways including in the human brain.^{4,13} [¹¹C]PMP was prepared in high radiochemical purity ($> 95\%$) by N-[¹¹C]methylation of piperidin-4-yl propionate using a previously described method.¹⁴ Dynamic PET scanning was performed for 80 minutes immediately after a bolus IV injection of 555 MBq (15 mCi) of [¹¹C]PMP. Emission data were collected in 21 sequential emission scans (6×30 seconds, 4×60 seconds, 2×90 seconds, 4×300 seconds, 5×600 seconds) in three-dimensional imaging mode using an ECAT HR+ tomograph (CTI PET Systems, Knoxville, TN), which acquires 63 transaxial slices (slice thickness = 2.4 mm, in-plane resolution = 4.1 mm full-width at half-maximum [FWHM]) over a 15.2-cm axial field of view. The scanner gantry was equipped with a Neuro-insert (CTI PET Systems) to reduce the contribution of scattered photon events.¹⁵ Before [¹¹C]PMP injection, a 10- to 15-minute transmission scan was acquired using rotating rods of [⁶⁸Ge/⁶⁸Ga] for attenuation correction of emission data.

An individually molded, thermoplastic mask was made for each subject to minimize head movement and facilitate accurate head positioning. The head was positioned such that the lowest scanning plane (visualized by a system of laser lines within the scanner gantry) was parallel to and 2.0 cm below the canthomeatal line. Each dynamic PET emission frame was reconstructed as a tomographic image volume of $128 \times 128 \times 65$ voxel matrix using the manufacturer-supplied software with at-

tenuation, scatter, dead time, and radioactive decay corrected using a Hanning filter with a frequency cutoff of 0.5 Nyquist. PET frames after the 3 minutes were coregistered to in-scanner head motion using the mutual information theory implemented in SPM2 (frame-to-frame head motion correction).

Data analysis. Volumes of interest (VOIs) were defined on the SPGR MRI with left and right hemispheres combined using in-house developed software (VOILand). The International Consortium of Brain Mapping template of VOIs¹⁶ was spatially normalized to the subjects' MRIs to provide predefined cortical VOIs covering the frontal, parietal, occipital, and temporal lobes. After manual corrections for errors associated with spatial normalization, if any, the VOIs were transferred from MRI space to PET space using MRI-to-PET coregistration parameters that were obtained with the mutual information theory¹⁷ as implemented in the intermodality coregistration module of SPM2.¹⁸ The striatum VOI was smoothed with a gaussian kernel (6.7 mm FWHM),¹⁹ and voxels with 1 were used to reduce partial volume effect to the reference region.²⁰ VOIs were applied on successive dynamic PET frames to generate time–radioactivity curves (TACs) of the regions. Gray matter TACs were obtained as follows to yield atrophy-corrected outcome variables. First, probability maps of gray and white matters and CSF were generated by an MRI segmentation routine of SPM2.¹⁸ The maps were transferred to PET space using the MRI-to-PET coregistration parameters and smoothed in the same manner as VOIs to reproduce smearing effects of PET.¹⁹ Weights of gray and white matters in VOIs (w_{GM} and w_{WM}) were obtained by applying the VOIs to white and gray matter maps. White matter TAC ($A_{WM}(T)$, one per scan) was obtained by applying a VOI consisting of high white matter probability voxels (>0.97) to PET frames. Gray matter TAC ($A(T)$) was obtained as follows: $A(T) = (A_{Obs}(T) - A_{WM}(T) \cdot w_{WM})/w_{GM}$, where $A_{Obs}(T)$ is observed TAC.

AChE hydrolysis rates (k_3) were estimated using a modification of the method proposed by Nagatsuka et al.²¹ using the striatal VOI (defined by manual tracing on SPGR MRI) as input function. The published operational equation in the method of Nagatsuka et al. is $A(T) = p_1 \cdot R(T) + p_2 \cdot \int R(t)dt - p_3 \cdot \int A(t)dt$, where $A(T)$ and $R(T)$ are atrophy-corrected radioactivity concentrations in VOIs and striatum. Two modifications were made.²² First, $R(T)$ was fixed at the highest mean of three consecutive frames for the later frames where $R(T)$ declined because of further metabolism beyond the hydrolysis. Second, p_3 was removed from the operational equation by fixing the $p_2:p_3$ ratio to the mean $A(T):R(T)$ ratio after 40 minutes when $A(T)$ reached respective plateaus in all regions. AChE hydrolysis rates were calculated for frontal, parietal, occipital, and temporal regions. Global cortical AChE hydrolysis rate was defined as the average of the frontal, temporal, parietal and occipital cortical activities.

Age-corrected Spearman rank partial correlation coefficients were calculated to evaluate the relationship between WMH and cortical AChE activity as well as clinical correlations. All statistical analyses were performed using the program SAS (SAS Institute Inc., Cary, NC).

RESULTS Community-dwelling, middle-aged and elderly subjects ($n = 18$; 11 women, 7 men) had a mean age of 71.0 ± 9.2 (range 55–84) years. The mean Mini-Mental State Examination (MMSE) score was 29.3 ± 1.0 (range 27–30). The mean severity score of bilaterally summed periventricular

Table 1 Age-corrected Spearman rank partial correlation coefficients between periventricular WMH and cortical AChE activity as determined by the scale of Scheltens et al.⁹

AChE activity	Periventricular WMH
Average cortex	$R = -0.51, p = 0.04$
Frontal lobe	$R = -0.31, p = 0.22$
Parietal lobe	$R = -0.35, p = 0.17$
Temporal lobe	$R = -0.51, p = 0.04$
Occipital lobe	$R = -0.58, p = 0.02$

AChE = acetylcholinesterase; WMH = white matter hyperintensities.

WMH on the scale of Scheltens et al. was 6.6 ± 3.4 (0–12), and that of nonperiventricular WMH was 14.8 ± 9.7 (10–36). The mean global cortical AChE k_3 hydrolysis rates was $0.0231 \pm 0.0019 \text{ min}^{-1}$. Increased age was associated with higher WMH ratings on the scale of Scheltens et al. ($R = 0.51, p = 0.03$). There was a nonsignificant trend toward a relationship between older age and lower cortical AChE activity ($R = -0.40, p = 0.10$).

Age-corrected Spearman rank correlation coefficients were used to evaluate the relationship between the periventricular and nonperiventricular MRI WMH ratings and AChE PET activity. Increased severity of periventricular ($R = -0.52, p = 0.04$) but not nonperiventricular ($R = -0.20$, not significant [NS]) WMH was related to decreased global cortical AChE activity. Regional cortical cholinergic effects of periventricular WMH were most significant for the occipital lobe ($R = -0.58, p = 0.02$; table 1 and figure 1). The correlation coefficient between total

Figure 1 Scatter plot of the relationship between periventricular WMH ratings and cortical AChE k_3 hydrolysis rates (min^{-1}) in the occipital lobe

AChE = acetylcholinesterase; WMH = white matter hyperintensities.

Table 2 Age-corrected Spearman rank partial correlation coefficients between cortical AChE activity and selected psychomotor, reaction time, and executive functions tests in an exploratory post hoc analysis

Test	Score, mean $\pm$ SD; range	$R_{(\text{age})}$
CPT-RT	451.0 $\pm$ 80.9; 335.9–677.1 ms	$R = -0.53, p = 0.03$
CPT-SE	6.6 $\pm$ 2.5; 3.4–12.4 ms	$R = -0.48, p = 0.07$
TMT-BA	62.3 $\pm$ 40.4; 18–161 s	$R = 0.35, \text{NS}$
Grooved pegboard	99.4 $\pm$ 30.8; 63–178 s	$R = 0.16, \text{NS}$

AChE = acetylcholinesterase; CPT-RT = Conners continuous performance test reaction time; CPT-SE = Conners continuous performance test standard error; TMT-BA = Trail Making Test B minus A; NS = not significant.

white matter lesion scores (combined periventricular and nonperiventricular) and cortical AChE activity ($R = -0.26, \text{NS}$) was not significant except for a nonsignificant trend for the occipital AChE activity ($R = -0.45, p = 0.09$).

Subgroup analysis limited to the frontal periventricular WMH Scheltens ratings, and global cortical AChE activity also demonstrated a significant inverse age-corrected correlation ($R = -0.51, p = 0.04$). Although there was no significant correlation between scores on the scale of Bocti et al. and global cortical AChE activity ($R = -0.34, \text{NS}$), there was a nonsignificant trend toward an inverse correlation between scores on the scale of Bocti et al. and AChE activity in the occipital lobe ($R = -0.45, p = 0.07$).

An exploratory post hoc analysis was performed to evaluate the functional significance of cortical AChE activity using tests from a selected psychomotor, information processing and executive function

battery. Results demonstrated inverse correlations between cortical AChE activity and the reaction time measure but not with the other tests (table 2).

DISCUSSION Our in vivo cholinergic imaging data indicate that severity of periventricular WMH is associated with lower cortical AChE activity in middle-aged and elderly subjects without dementia. In contrast, there was no significant effect of nonperiventricular WMH on global cortical AChE activity. The present study provides evidence for disruption of cholinergic output fibers from the nbM by strategically located white matter lesions resulting in cortical cholinergic deafferentation, as illustrated in figure 2. It should be noted, however, that this study was cross-sectional in nature, and hence no conclusions about causality of the reported associations can be made.

Previously designed rating scales to rate strategic locations of WMH that may disrupt cholinergic projection fibers, such as the scale of Bocti et al., have a main focus at the lateral cholinergic pathway.¹¹ The main forebrain cholinergic bundle supplying both the medial and lateral pathways closely loops around the anterior corpus callosum and the frontal horns of the ventricles. Frontal horn periventricular WMH, particularly at the inferior aspect, may also affect the integrity of the adjacent medial cholinergic pathway. The periventricular subscale of the scale of Scheltens et al., therefore, accounts for white matter pathology that is relevant to not only the lateral but also the medial cholinergic pathways. This is supported by our data where we found more robust associations with the periventricular subscale of Scheltens et al. and cortical AChE activity compared with ratings obtained from the scale of Bocti et al.¹¹ Subgroup analysis limited to the frontal periventricular WMH ratings and global cortical AChE activity demonstrated similar findings compared with total periventricular ratings. Visual detection of frontal horn white matter disease, so-called capping, may thus serve as a simplified screening biomarker for functionally more significant leukoaraiosis that may disrupt cholinergic pathways.

The severities of periventricular and nonperiventricular white matter lesions are significantly correlated with each other.^{23,24} However, our findings of a predominant association between increased severity of periventricular lesions and decreased cortical AChE activity merely reflect the strategic anatomic location of periventricular lesions in close proximity to cholinergic projection pathways.

As fibers entering the cerebral hemispheres from the frontal forebrain radiate fan-like through the cerebral white matter to the cortex, their density per

Figure 2 Diagram to illustrate the “fiber disruption” hypothesis of cholinergic projection axons caused by white matter lesions, especially those in the periventricular forebrain close to the nucleus basalis of Meynert (gray)

Disrupted cholinergic projection axons are presented by a dashed line. WMH = white matter hyperintensities.

unit of brain tissue volume decreases along the way from their source to destination.²⁵ Thus, longer fibers that project to more posterior cortical regions may be at higher risk of disruption than shorter fibers within the frontal lobe. This notion is supported by our data where cholinergic deafferentation effects were most significant for the occipital region and not significant for the frontal lobe.

Although cholinergic neuronal loss in the nbM has been recognized as a significant pathology in AD, small vessel cerebrovascular disease may increase the likelihood of expressing dementia in those with co-occurring AD pathology.²⁶ For example, the presence of WMH, especially those that may disrupt cholinergic pathways, has been found to significantly contribute to cognitive, especially executive, impairment in patients with AD.^{11,27} A recent study also found evidence of a synergistic detrimental effect between global atrophy (global marker of AD) and more severe WMH on the rate of cognitive decline in patients diagnosed with AD.²⁸

We also performed an exploratory post hoc analysis to evaluate the functional significance of cortical cholinergic deafferentation using tests from a selected psychomotor, information processing and executive function battery. Preliminary results demonstrated significant inverse correlations between cortical AChE activity and choice reaction time. It should be noted that the correlation coefficients were modest. This may reflect the somewhat narrow range of cognitive test performance in the study participants with MMSE scores in the reference range of 27 to 30. A previous study found that elderly with higher drug-related serum anticholinergic activity had psychomotor slowing including response time, suggesting a central role of the cholinergic system in information processing.²⁹ Unlike our previous findings in patients with Parkinson disease or AD,^{30,31} we did not find evidence of a relationship between cholinergic cortical activity and executive cognitive function in this study. It is unclear whether a threshold of cholinergic denervation exists below which more pure cognitive executive deficits would manifest. Our small sample size did not allow multivariate statistical analysis to study effects of potential confounding variables, such as education or sex.

It should be noted that the cortical AChE activity in our subjects fell in the range of predominant normal variability seen with aging and well above pathologic disease states. Future studies are needed to expand the study population to include patients with vascular dementia and to study specific cognitive effects of cortical cholinergic functions in the presence of more severe leukoaraiosis.

AUTHOR CONTRIBUTIONS

Statistical analyses were conducted by N.I.B. and G.M.C., Department of Mathematics and Statistics, University of Pittsburgh, PA.

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