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White Matter Hyperintensities in Mild Cognitive Impairment and Lower Risk of Cognitive Decline

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Abstract.
Background: White matter hyperintensities (WMH) may have a different impact on cognitive decline depending on strategic localization.
Objective: The goal of this study is to assess the impact of global and cholinergic WMH on cognitive decline of mild cognitive impairment (MCI) patients in the ADNI-1 dataset.
Methods: This is a retrospective analysis of data from a natural history study. MRI scans (T2 and PD sequences) were assessed with two visual scales: 1) The Cholinergic Pathways HyperIntensities Scale (CHIPS) score, designed to assess WMH in the cholinergic tracts, and 2) the Age-Related White Matter Changes Scale (ARWMC), a scale to assess the global WMH burden. All subjects underwent standardized neuropsychological testing.
Results: Subjects included 310 individuals with MCI. Analysis showed no association between WMH at baseline and conversion from MCI to Alzheimer's disease (AD), either for the global WMH burden or WMH within the cholinergic pathways. However, ARWMC scores had a significant confounding effect ($p = 0.03$) on conversion to dementia (hazard ratio of 0.37) among MCI subjects with low executive functions.
Conclusion: We found no association between the burden of WMH at baseline in MCI and conversion to AD over 3 years. However, a higher global WMH burden appears to reduce the risk of conversion to AD in subjects with low executive functions. These results suggest that higher WMH burden in MCI individuals may be associated with a more gradual cognitive decline or stabilization, compared to a low WMH burden.

Keywords: ADNI, Alzheimer's disease, cholinergic pathways, executive functions, mild cognitive impairment, white matter hyperintensities

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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INTRODUCTION

Small vessel disease is evident in a high proportion of normal elderly volunteers. This has been reported in population studies as lacunar strokes on T1-weighted magnetic resonance imaging (MRI), occurring in 28% of individuals [1], or as subcortical white matter hyperintensities (WMH) seen on T2 -weighted MRI in up to 95% of those over 65 [2]. These lesions may result from vascular mechanisms including vascular occlusions, hypoperfusion, or occlusive venous collagenosis [3]. Vascular pathology has been detected in up to 80% of the brains of older adults in population based autopsy series [4].

Thus, WMH are common radiological findings in elderly individuals, whether or not they present cognitive impairment [1–4]. Studies have shown decline in executive functions [5, 6], memory [7] and global cognition [8] in patients with mild cognitive impairment (MCI) and WMH. However, the association between WMH and MCI remains uncertain, and some studies have shown no such association [9–10], with a recent meta-analysis showing conflicting results [11]. Furthermore, the effect of WMH on the evolution of executive function decline is still poorly understood.

Localization of WMH might be a factor contributing to this heterogeneity, associating specific changes in cognition with WMH in certain loci [12]. A possible mechanism by which WMH may impact cognition is by interference with projecting tracts of modulating neurotransmitters, such as the cholinergic system [13–15].

The goal of this study was to assess the impact of WMH on cognitive decline, more specifically on executive functions, in the Alzheimer's Disease Neuroimaging Initiative 1 (ADNI-1) dataset. We measured global WMH burden using the Age-Related White Matter Changes Scale (ARWMC) [16] and WMH within the cholinergic tracts with the Cholinergic Pathways HyperIntensities Scale (CHIPS) [13].

MATERIALS AND METHODS

Standard protocol approvals, registrations, and patient consents

The institutional review boards of all participating institutions approved the procedures for this study. Written informed consent was obtained from all participants or surrogates. More information about ADNI investigators is given in the Acknowledgment section. Information pertaining to the ADNI-1 cohort and biomarker information collection and analysis is available via the ADNI website (http://adni.loni.usc.edu) and publications [17].

Study design

This is a retrospective analysis of data from a non-randomized, natural history non-treatment study.

Data used in the preparation of this article were obtained from the ADNI database (http://adni.loni.usc.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies, and non-profit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early Alzheimer's disease (AD). Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The Principle Investigator of this initiative is Michael W. Weiner, M.D., VA Medical Center and University of California – San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these three protocols have recruited over 1,500 adults, ages 55 to 90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow up duration of each group is specified in the protocols for ADNI-1, ADNI-2, and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date information, see http://www.adni-info.org.

Subjects

The ADNI-1 study was designed to define the rate of progression of MCI and AD and to reproduce the characteristics of treatment trials. It is a longitudinal study comprising cognitive testing, biomarkers and MRI scans (at baseline and 6, 12, 24, 36, and 48 months later). All 55- to 90-year-old subjects with

MCI were enrolled and followed-up at 59 centers in the US and Canada, starting in 2005. ADNI-1 patients were screened using both Mini-Mental State Examination (MMSE) [18] and Clinical Dementia Rating (CDR) [19] scales. Patients were excluded if they had scores of 4 or greater on the Hachinski ischemic scale [20], history of structural brain lesions or trauma, or if they used specific psychoactive medication (such as anti-depressants or narcoleptics with anti-cholinergic properties, regular narcotic analgesics, or anti-parkinsonian medication).

For this study, we selected from ADNI-1 only MCI subjects that had (a) at least two clinical follow-ups during 36 months (cf. section Cognitive assessment and diagnosis); (b) baseline MRI images (cf. section Baseline image acquisition); and (c) have no missing values on the Trail Making Test B for executive function. Subjects who reverted back from MCI to normal were not included in the analysis.

Cognitive assessment and diagnosis

The cognitively normal group was defined as individuals with MMSE scores 24 to 30, a CDR Scale score of 0, and no evidence of major depression, MCI, or dementia. Patients were classified in the MCI group if they had subjective memory complaints and objective deficit in memory as measured by the Wechsler Memory Scale-Revised Logical Memory II [21] scores, a CDR score of 0.5, no impairment of significance in other cognitive areas, preserved activities of daily living, and no diagnosis of dementia. Participants were classified as AD if they had an MMSE score of 18 to 26, a CDR score of 0.5 to 1.0, and met the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer Disease and Related Disorders Association [22] criteria for probable AD. The ADNI-1 subjects underwent cognitive evaluation according to a standardized protocol. This protocol included the Auditory verbal learning test [23], the Logical memory test [21], and the Trail Making Test [24].

Baseline image acquisition

Baseline image acquisition was done using a strict protocol that was validated at each individual site, including the use of a fluid filled phantom before each scan, and rapid gradient echo sequences [25]. High resolution 1.5T T1-weighted sagittal volumetric magnetization prepared rapid gradient echo (MP-RAGE) and axial proton density/T2-weighted fast spin echo sequences were analyzed.

Baseline image analysis

General WMH rating scale

The ARWMC scale uses a four-point system to evaluate radiological severity (0 = normal; 1 = punctuate lesion(s); 2 = beginning confluence; 3 = diffuse involvement) in 10 key regions of the brain (right and left frontal, parieto-occipital, temporal, infratentorial, and basal ganglia) [16]. Regional scores are added for a total of 30 points. This scale was used as a measure of general WMH.

Cholinergic tract WMH

CHIPS was developed and validated by one of the authors [13]. This scale is based on anatomical landmarks from immunohistochemical studies and evaluates WMH in the medial and lateral cholinergic pathways. It uses a three-point system (0 = normal; 1 = <50% involvement; 2 ≥ 50% involvement) at four different standardized axial levels on the MRI scans, with a factor of 4 attributed to the lower level and decreasing factors for each successive higher levels, to account for decreasing fiber density. Each of the following levels have separate ratings for the anterior and posterior regions: the lower external capsule, the higher external capsule, the corona radiate, and the centrum semiovale. The maximum possible score is 50 for each hemisphere, for a total of 100 points. Every T2 and proton density MRI sequence was assessed blind to outcome, and 20 scans were assessed by two raters trained in neurology including a clinical neurologist and a neurology resident for interrater agreement.

Hippocampal volume

Hippocampal volumes were measured using semi-automated hippocampal volumetry with the Medtronic Surgical Navigation Technologies high dimensional brain mapping tool (http://www.medtronic.com/for-healthcare- professionals/ products- therapies/ spinal/ surgical-navigation-imaging/surgical-navigation-systems/).

Cerebrospinal fluid (CSF) biomarkers

CSF samples were collected in a number of patients and were then batch-processed using a standardized protocol (http://adni.loni.usc.edu). Analysis was carried out using a Luminex instrument. Tested biomarkers included CSF amyloid-β $(A\beta)_{1\text{-}42}$ and t-tau.

Statistical analyses

Study variables

Descriptive statistics are presented for all study variables. We assessed distribution normality and used Student's T or Wilcoxon tests accordingly to compare quantitative variables. We computed an intraclass coefficient to evaluate interrater agreement between the two raters for the ARWMC and CHIPS scales.

WMH and cognitive decline

Conversion from MCI to AD over the first three years of the ADNI-1 study was the primary outcome. We verified the association between WMH and conversion from MCI to AD with a non-parametric Wilcoxon statistic (due to the non-normality of the data) and Kaplan-Meier survival curves. Subjects were divided in two WMH groups as determined by their inclusion in either the first two or last two quintiles on the ARWMC score. To better contrast the impact of WMH, the third quintile was eliminated from data (49 subjects).

Executive function, WMH, and cognitive decline

Subjects were then divided in two executive function groups (low or high) in the same way as determined by their belonging to either first two or last two quintiles on the Trail Making Test part B. We used Pearson's r statistic to test the linear correlation between ARWMC and CHIPS.

We used Kaplan-Meier survival curves to compare graphically the rate of progression from MCI to AD between low and high executive functions groups. We used the Log-Rank and Wilcoxon tests to compare analytically the difference between these groups. To respect the assumption of proportionality, we used the stratified Cox survival analysis on the whole cohort ($n = 245$) with robust variance estimators for correlated observations to examine the contribution of WMH dichotomized as explained above. We also included other co-variates in the model, such as hippocampal volumes, CSF $A\beta_{1\text{-}42}$ and t-tau, age, and education, when available.

Statistical analyses were executed using a statistical significance threshold of 0.05.

All analyses were performed using SAS version 9.3.

RESULTS

Inter-rater agreement

The interrater agreement coefficients between the two raters were very good for both the general WMH scale (ARWMC ICC = 0.93) and the cholinergic tract WMH scale (CHIPS ICC = 0.81).

WMH impact on conversion from MCI to AD

We included 310 individuals with MCI in the first analysis. Of these, 124 progressed to probable AD (MCIp) and 186 remained stable (MCIs). Table 1 reports demographic characteristics at the time point of conversion for MCIp or the last follow up for MCIs.

We included 259 of the 310 individuals with MCI in the first analysis when dichotomized in the first two and last two quintiles of WMH. There was no significant difference between groups for gender ($p = 0.79$), education ($p = 0.52$), hippocampal volume ($p = 0.08$), CSF $A\beta_{1\text{-}42}$ ($p = 0.17$), and CSF t-tau ($p = 0.99$) (Table 2). We found a significant difference for age ($p < 0.01$).

Almost half (47.8%) of all MCI subjects had few or no WMH (ARWMC <2). Survivor curves and two-sample Wilcoxon statistics for conversion from MCI to AD did not statistically differ (ARWMC $p = 0.51$ and CHIPS $p = 0.87$).

Table 1
Patient characteristics according to their conversion status from MCI to AD. Mean ± SD for quantitative and % of females for gender

	Status		
Variable (#subjects)	MCIs	MCIp	*p*-value
Gender in % F ($n = 310$)	35.5%	39.5%	0.47
Age in years ($n = 310$)	77.04 ± 7.49	76.33 ± 7.29	0.39
Education in years ($n = 310$)	15.59 ± 3.09	15.90 ± 2.81	0.47
Trail making test B in scores ($n = 310$)	127.26 ± 74.96	178.09 ± 91.73	<0.01
ARWMC in scores ($n = 310$)	2.20 ± 2.50	2.55 ± 2.95	0.43
Chips in scores ($n = 310$)	5.48 ± 7.77	6.00 ± 8.91	0.69
Hippocampal volume in mm^3 ($n = 244$)	3171.22 ± 52.39	2865.75 ± 496.87	<0.01
$A\beta_{1\text{-}42}$ ($n = 35$)	198.35 ± 54.33	155.93 ± 55.75	0.03
T-tau ($n = 38$)	82.32 ± 44.87	108.44 ± 43.08	0.03

MCIs, mild cognitive impairment patients who remained stable; MCIp, mild cognitive impairment patients who progressed to probable Alzheimer's disease.

Table 2
Patient characteristics according to their WMH load

	Group of WMH			
Variable (#subjects)	WM < quintile 3	WM > quintile 3	WM quintile 3	*p*-value*
Gender in % F ($n = 259$)	35.26%	36.89%	43.14%	0.79
Age in years ($n = 259$)	75.44 ± 7.73	78.58 ± 7.16	77.10 ± 6.06	<0.01
Education in years ($n = 259$)	15.92 ± 2.88	15.67 ± 3.15	15.18 ± 2.94	0.60
Chips in scores ($n = 259$)	4.24 ± 3.22	8.75 ± 10.64	3.91 ± 5.52	<0.01
Trail B in scores ($n = 259$)	136.00 ± 81.00	149.90 ± 91.84	147.94 ± 82.17	0.01
Hippocampal volume in mm^3 ($n = 195$)	3084.20 ± 554.60	2950.10 ± 493.90	3020.94 ± 523.23	0.08
$A\beta_{1\text{-}42}$ ($n = 30$)	189.10 ± 54.81	165.20 ± 67.89	184.20 ± 47.55	0.18
T-tau ($n = 33$)	91.40 ± 44.71	113.85 ± 51.74	94.40 ± 39.28	0.99

*p-value pertains to the comparison between 2 groups: WM > quintile 3 and WM > quintile 3.

Table 3
Patient characteristics according to their executive functions trail making test part B

	Group of trail making test part B			
Variable	High exec. functions (< quintile 3)	Low exec. functions (> quintile 3)	Quintile 3	*p*-value*
Gender in % F ($n = 245$)	38.84%	37.10%	33.85%	0.78
Age in years ($n = 245$)	76.31 ± 7.22	76.48 ± 7.89	78.12 ± 6.68	0.86
Education in years ($n = 245$)	16.21 ± 2.61	14.98 ± 3.30	16.17 ± 2.74	<0.01
ARWMC in scores ($n = 245$)	2.20 ± 2.46	2.35 ± 2.61	2.62 ± 3.22	0.64
Chips in scores ($n = 245$)	5.09 ± 6.62	5.42 ± 7.24	7.30 ± 11.87	0.62
Hippocampal volume in mm^3 ($n = 195$)	3127.02 ± 583.68	2976.27 ± 518.55	2962.55 ± 431.08	0.06
$A\beta_{1\text{-}42}$ ($n = 30$)	199.88 ± 61.23	161.00 ± 50.94	170.80 ± 57.57	0.07
T-tau ($n = 33$)	81.00 ± 34.96	113.25 ± 52.25	71.40 ± 33.86	0.04

*p-value pertains to the comparison between 2 groups: WM > quintile 3 and WM > quintile 3.

Executive function impact on conversion from MCI to AD

When dichotomized according to executive function, only 245 participants were included due to availability of information (Table 3). The higher executive functions group had, as expected, higher education ($p < 0.01$). This group also had lower CSF t-tau ($p = 0.04$), and a trend toward higher hippocampal volume and CSF $A\beta_{1\text{-}42}$.

The Kaplan-Meier survival curve shows that patients with low executive functions (higher time to complete the Trail Making Test Part B), have a higher conversion rate than those with high executive function (lower time) - see Figure 1. The difference between the curves is tested by Log-Rank ($p < 0.01$) and Wilcoxon ($p < 0.01$).

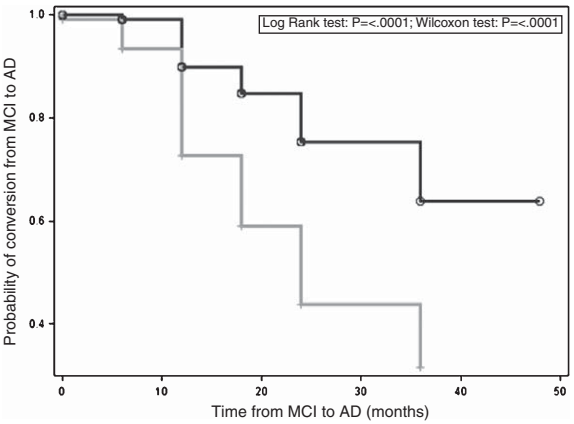

Fig. 1. Survival curves of conversion from MCI to AD according to executive functions (trail making test). Legend: Black: high executive functions; Gray: low executive functions.

Table 4 reports all variables included in the Cox model to show the effect and the risk ratio on patient's conversion from MCI to AD. CHIPS had to be eliminated from this model because it was highly correlated with ARWMC (Spearman Correlation = 0.917; $p < 0.01$). The Cox model obtained using CHIPS as a covariable of interest is available in the Supplementary Material as Table 1. ARWMC, the covariable of interest, has a significant effect ($p = 0.03$) on the conversion with a hazard ratio of 0.37. This means that, if ARWMC increases by one unit, the relative risk of conversion from MCI to AD decreases by 63%, all other covariables remaining unchanged. This effect remained significant even after adjustment for the level of education.

Table 4
Estimation parameters and risk ratio of covariables included in the ARWMC Cox model

Covariable	Parameter estimate	Chi-square	*p* value	Risk ratio (95% CI)
Age	−0.05	0.36	0.55	0.95 (0.81–1.12)
Education	−0.62	5.00	0.03	0.54 (0.31–0.93)
ARWMC	−1.00	4.62	0.03	0.37 (0.15–0.92)
Hippocampal Volume	0.00	0.18	0.67	1.00 (0.99–1.00)
T-tau	−0.03	2.89	0.09	0.97 (0.95–1.00)
$A\beta_{1\text{-}42}$	−0.00	0.00	0.98	1.00 (0.98–1.02)

DISCUSSION

This study showed no association between WMH and conversion to AD in patients with MCI in the ADNI-1 study when considered alone. This was true for either general WMH burden or WMH in the cholinergic tracts. These negative results might be explained by the generally low WMH burden of the patients included in ADNI-1. The patients of the ADNI-1 cohort were selected to have little vascular risk factors; subjects with a Hachinski Ischemic score of 4 or greater and a prior history of cerebrovascular disease were excluded. This low vascular risk was corroborated by the present study, where average WMH scores are very low (mean CHIPS score 5.61). This is in contrast to a study showing correlation between CHIPS score and cognitive functions, where WMH burden was much higher (mean CHIPS score in vascular MCI patients 34.28) [15]. As a result, these findings might not be generalized to a patient population with more vascular risk factors.

An association between WMH and executive functions in the ADNI-1 cohort has been reported using volumetric measurements of WMH [26]. However, the cognitive tests used to measure executive functions were arguably not purely "executive"; indeed, the authors used a composite score including category fluencies, the digit symbol substitution test and the backward digit span, but also the forward digit span, which better represents simple attention span. The use of the Trail Making Test part B as a measure of executive functions represents an easy, quick, and widely used way of testing executive functions. It is efficient and sensitive to brain impairment, and provides a good measure of executive control function [27].

Analyses of patients dichotomized according to performance of executive functions showed a greater tendency of patients with MCI and low executive functions to progress to AD. This is not a new finding, and this has been noted in a recent meta-analysis [28]. A more surprising finding is that, in the present analysis, a higher general WMH burden seemed to reduce the risk of conversion to AD when subjects were dichotomized for executive functions. This seems to suggest that a higher vascular burden in MCI is associated with less progression than MCI without WMH, where degenerative changes would presumably be the most important factor, and thus more likely to progress to AD. The same phenomenon was observed in a recent report [29]. Similar results were also reported in another longitudinal study showing a decline in executive functions and an increased rate of conversion to dementia in degenerative (hippocampal atrophy) versus vascular (WMH) MCI [30]. However, since the ADNI database excluded particular groups of patients described above, results reported in this publication may be partially driven by selection bias. In the light of this bias, results of this study cannot be generalized to populations differing from the ADNI sample.

One of the limits of this study is the use of the ARWMC scale for general WMH as opposed to volumetric estimates of WMH. However, this scale has been shown to correlate well with volumetry. A ceiling effect of rating scales as compared to volumetry for higher WMH burden was reported, but as subjects in the ADNI-1 cohort have a small WMH burden, this limit is not likely to influence our results [31]. Another limit is the lack of consideration of vascular risk factors such as blood pressure. However, these risk factors might not have been measured consistently. They are also susceptible to much variation with possible changes of treatment of these conditions over the years of follow-up of the ADNI-1 cohort. This could affect the results in an unpredictable way. Finally, because of the 36 month follow-up limit, some patients might have converted to AD past the cut-off time of our study. Results only reflect this time period.

The major strong point of this study is the size and the prospective nature of the ADNI-1 cohort, which is to date one of the largest available cohorts for the study of cognitive performance and radiologic findings in the context of MCI and AD.

This study showed that a higher global WMH burden appears to reduce the risk of conversion to AD in MCI subjects with low executive functions in the ADNI-1 cohort. These results suggest that a higher WMH burden in MCI individuals may be associated with stabilization or more gradual decline. These results might help better understand the role of vascular lesions in cognition.

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SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/JAD-140618.

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