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RESEARCH ARTICLE

White matter hyperintensity, neurofilament light chain, and cognitive decline

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Abstract

Objective: We aimed to determine whether combining white matter hyperintensity (WMH) with neurofilament light chain (NfL) could provide additional information for cognition in older adults. **Methods**: Utilizing data from the population-based Chicago Health and Aging Project, we studied 701 individuals with both biomarkers and cognitive data during the follow-up period. NfL was measured using an ultrasensitive immunoassay, single-molecule array technology. MRI scans of the brain were acquired using 1.5-T systems. Global cognitive function was created as a composite measure of four neuropsychological tests, standardized and averaged to *z*-scores. Multivariable linear mixed-effects models were used to evaluate the association of WMH and NfL with the rate of cognitive decline. **Results**: Higher WMH and NfL were associated with a faster rate of cognitive decline during the follow-up; β-coefficients (95%CIs) were −0.011 (−0.02, −0.001) and −0.010 (−0.017, −0.003), respectively. In individuals with lower concentration of NfL (i.e., bottom tertile), a higher WMH volume was associated with a faster cognitive decline (β: −0.030; 95%CI −0.046, −0.014). Similarly, in individuals with lower volumes of WMH (i.e., bottom tertile), a higher concentrations of NfL was associated with a faster cognitive decline (β: −0.023; 95%CI −0.042, −0.005). When we combined WMH with NfL, we noted a graded association with increasing volumes of WMH, particularly in people with lower NfL values. **Interpretation**: While both biomarkers, WMH and NfL, were similarly associated with the annual rate of cognitive decline, our study suggests that they provide different underlying mechanisms affecting cognition.

Introduction

Early identification of individuals at higher risk of Alzheimer's disease offers an opportunity for targeted intervention,[1,2] particularly when evidence supports early intervention as a strategy that may halt or postpone disease occurrence.[3,4] With advances in dementia research, novel biomarkers have been developed and have contributed to the early identification of older adults at risk of Alzheimer's disease.[5] These biomarkers range from neuroimaging to the concentrations of proteins of neurodegeneration in blood or cerebrospinal fluid samples. For example, we have recently shown that neurofilament light chain (NfL) assessed in the blood is associated with cognitive decline in older adults and may predict the development of Alzheimer's disease.[6] NfL is a protein located in the cytoplasm of neurons and expressed in myelinated axons. An increase in NfL in the blood may result from neuron damage.[7] In addition to neuron damage, neuroimaging biomarkers may also offer information on the vascular disease of the brain, such as cerebral small vessel disease. Cerebral small vessel disease is detected on magnetic resonance imaging (MRI) as white matter hyperintensities (WMHs). Research studies have

consistently shown a dose-dependent relationship between WMH, cognitive decline, and risk of Alzheimer's disease.[8,9] While both biomarkers (NfL and WMH) are related to cognitive functioning and dementia risk, they may present different pathways and mechanisms for dementia. In addition, they differ in the assessment method, which includes the procedures (blood draw versus undergoing MRI scanning), costs, and availability in clinical settings. However, from the clinical research perspective, we are interested in knowing whether these biomarkers complement each other or whether one biomarker is more advantageous than the other, regardless of cost and availability.

Therefore, this study aims to prospectively investigate the association of NfL and WMH with cognitive decline. In addition, we will determine whether the combination of both biomarkers could provide additional information for cognition in older adults enrolled in a population-based study.

Methods

Study design, settings, and population

The Chicago Health and Aging Project (CHAP) is a population-based cohort study investigating the risk factors for cognitive impairment and Alzheimer's disease and related dementias.[10] CHAP recruited 10,802 participants in four biracial Chicago neighborhoods based on a door-to-door census. Data collection occurred in 3-year cycles between 1993 and 2012, consisting of four successive cohorts with the enrollment of African Americans and White residents living in the same geographical area and who reached the age of 65 years during the study.[10] Of 10,802 participants, a stratified random sample, approximately one-third of all participants (n = 2932), was selected for clinical evaluations to diagnose Alzheimer's disease. The Institutional Review Board of the Rush University Medical Center approved the CHAP study, and all participants provided written informed consent.

Blood samples were drawn among 5696 participants during the study duration from 1993 to 2012. Due to cost and budget constraints, immunoassays for measuring NfL were performed on 1323 participants with cognitive data.[6] From 2000 to 2012, participants with clinical evaluation for Alzheimer's disease were invited for an MRI scan.[11] Of 2932 participants, 1235 were invited for MRI assessment, and 975 provided informed consent. Of 975 individuals, 923 had data on WMH and cognitive scores. We also identified individuals in our study with data on NfL, WMH, and cognition comprising 701 individuals.

Assessment of demographics and other confounders

Age was computed from the self-reported birth date and the date when blood was drawn. Race/ethnicity and sex were assessed by participants' responses to the structured questions of the 1990 US Census.[12] Years of regular schooling were self-reported and used to assess education. The APOE genotypes were determined based on the single nucleotide polymorphisms (SNPs) of the rs7412 and rs429358 measured by the Broad Institute Center for Genotyping using the hME Sequenom MassARRAY platform.[13]

Assessment of WMH

WMH is assessed on a combination of FLAIR and 3D T1 MRI images using a modified Bayesian probability structure.[14] Three imaging sequences using fluid-attenuated inversion recovery, SPGR with an echo-time minimum, double-spin echo with a repetition time of 2100 ms.[15] These MRI images are for research purposes. Likelihood calculations of the original image are calculated through histogram segmentation and thresholding.[16] Probability likelihood values of WMH at each voxel in the white matter are thresholded at 3.5 SD above the mean to create a binary white matter hyperintensity mask. The segmented WMH masks are then back-transformed to native space for tissue volume calculation.[14] WMH volumes (cc) were corrected for the total cranial volume to account for the head size and then were log-transformed to normalize variance.

Assessment of NfL

Unthawed blood samples were sent to Quanterix Corporation, where NfL was assayed in duplicates through the single-molecular assay bead-based HD platform and the Neurology 4Plex A kit. We evaluated the mean concentration of NfL for duplicate measurements in this analysis, and the coefficient of variation among duplicates was 3.0%.[6]

Assessment of global cognitive function

During in-home interviews, in each CHAP cycle, four neuropsychological tests of cognitive function were conducted: immediate and delayed recall of a brief story[17,18]; the Symbol Digit Modalities Test,[19] a measure of the perceptual speed[20]; and the Mini-Mental State Examination.[21] We calculated z-scores for each test using baseline means and SDs for the entire CHAP sample.[22] A composite z-score was created by averaging all four tests. A

positive *z*-score indicates better cognitive performance than the population's average, and a negative score means poor cognitive function.

Statistical analysis

Characteristics of the study population are presented as mean and standard deviation (SD) for continuous variables and number and percentage for categorical variables. Multivariable linear mixed-effects regression analyses were performed to evaluate the association of WMH and NfL with cognitive decline during the study period. Models were adjusted for age, sex, race, education, APOE4, and interaction with time (i.e., lag). The interaction term with time allows us to determine the annual rate of change. We investigated both linear (continuous variable, log10 transformed) and non-linear (tertiles) associations of WMH and NfL with cognitive decline.

We conducted three consequential analyses to determine whether NfL and WMH are similarly associated with the rate of cognitive decline in older adults, whether one biomarker offers additional information about cognition, or whether the combination of both biomarkers may better predict the rate of cognitive decline. First, we investigated the association of NfL and WMH with cognitive decline in the overall study sample. Second, we focused on each category or tertile of one biomarker (e.g., NfL) and determined the relationship of the other biomarker (e.g., WMH) with cognitive decline separately on each tertile (category). This analysis allows us to explore the heterogeneity within each category/tertile of the biomarker. Third, we combined tertiles of NfL and WMH, creating nine groups and evaluated the rate of decline by comparing people with different levels of NfL and WMH to individuals with low values (tertiles) of NfL and WMH.

Analyses were conducted using the R program, version 4.1 (R Group for Statistical Computing, Vienna).

Results

Table 1 shows the characteristics of the study population in participants with data on NfL serum concentration (n = 1323), individuals who underwent an MRI scan and assessed WMH (n = 923), and subjects with overlapping data on both variables NfL and WMH (n = 701). Focusing on the sample of 701 participants with WMH and NfL data, the mean age was 78.1 years (SD = 5.9), and 61% were women. On average, participants had 12.9 (SD = 3.5) years of schooling. The Spearman's correlation coefficient between WMH and NfL was r = 0.23.

The association of NfL and WMH, as continuous and categorical variables, with cognitive decline during the follow-up, is shown in Table 2. Higher concentrations of NfL and WMH volumes were associated with a faster decline in cognitive functioning. Among 1323 participants with blood measures of NfL, a 1-SD increase in log10 NfL is significantly associated with a faster cognitive decline by 0.010 units/year (β: −0.010; 95%CI −0.017, −0.003). Also, compared to the first tertile of NfL (reference group), individuals in the third tertile had a faster cognitive decline by 0.026 units/year (β: −0.026; 95%CI −0.042, −0.009). Among 923 individuals with measures of WMH, a 1-SD increase in log10 WMH was associated with a faster cognitive decline by 0.011 units/year (β: −0.011; 95%CI −0.02, −0.001). Compared to individuals in the first tertile of WMH volumes, those in the third tertile had a faster rate of decline by 0.030 units/year (β: −0.030; 95%CI −0.053, −0.007).

Table 3A presents the association of WMH with cognitive decline among individuals with different levels (e.g., tertiles) of NfL. Table 3B shows the association of NfL with cognitive decline in participants with different levels of WMH volumes. Across tertiles of NfL, WMH was

Table 1. Demographic and clinical characteristics of the study population.

	WMH and NfL sample	WMH sample	NfL sample
n	701	923	1323
Age, years	78.1 (5.9)	79.4 (6.2)	78.7 (6.3)
Sex, *n* (%)			
Women	427 (60.9)	568 (61.5)	822 (62.1)
Men	274 (39.1)	355 (38.5)	501 (37.9)
Race, *n* (%)			
Whites	261 (37.2)	365 (39.5)	515 (38.9)
African Americans	440 (62.8)	558 (60.5)	808 (61.1)
Education, years	12.9 (3.5)	13.1 (3.5)	12.5 (3.6)
APOE4 allele, *n* (%)			
Non-carriers	468 (66.8)	621 (67.3)	874 (66.1)
Carriers	233 (33.2)	302 (32.7)	449 (33.9)
Global cognition, *z*-score	0.3 (0.6)	0.3 [−0.1, 0.7]	0.2 [−0.3, 0.7]
MMSE score	28.0 [26.0, 29.0]	27.1 (3.3)	26.0 (4.7)
WMH, volume	8.5 [3.2, 19.6]	7.7 [3.0, 19.0]	–
Total cranial volume	1155.6 [1073.7, 1251.2]	1163.7 [1080.1, 1255.7]	–
NfL, pg/mL	23.8 [17.6, 33.5]	–	25.5 [18.5, 37.3]

For continuous variables, data are shown as mean (standard deviation) or median [inter-quartile range]; for categorical variables, data are given as absolute numbers (proportions).
APOE, apolipoprotein E; NfL, neurofilament light; WMH, white matter hyperintensities.

Table 2. Association of NfL and WMH with cognitive decline during follow-up.

	NfL				WMH			
	N	Median	Beta	95%CI	*N*	Median	Beta	95%CI
Continuous	1323	25.5	−0.010	−0.017, −0.003	923	7.7	−0.011	−0.02, −0.001
Categorical								
T1	439	16.1	0.000	Reference	305	1.9	0.000	Reference
T2	434	25.4	−0.006	−0.021, 0.01	304	7.6	−0.014	−0.035, 0.008
T3	450	44.3	−0.026	−0.042, −0.009	314	25.0	−0.030	−0.053, −0.007

Continuous indicate 1 standard deviation increase in log10 transformed NfL or WMH. Adjusted by age, sex, race, education, and APOE4. Beta estimate and (95%CI) is time interaction of NfL or WMH.

Table 3. Association of WMH and NfL with cognitive decline within tertiles of NfL and WMH.

Exposure	*N*	Tertiles of NfL	Median NfL [IQR]	Median WMH [IQR]	Beta	95%CI
A: Association of WMH with cognitive decline on each tertile of NfL						
Continuous WMH	270	T1	16.5 [13, 18.6]	5.4 [2.2, 14.2]	−0.030	−0.046, −0.014
Continuous WMH	223	T2	24.9 [22.6, 27.1]	8.4 [3.9, 21.7]	−0.002	−0.024, 0.02
Continuous WMH	208	T3	41.8 [36, 53.9]	12.2 [5.2, 24]	0.009	−0.015, 0.033
Exposure	*N*	Tertiles of WMH	Median WMH [IQR]	Median NfL [IQR]	Beta	95%CI
B: Association of NfL with cognitive decline on each tertile of WMH						
Continuous NfL	220	T1	2 [1, 3]	20 [15.4, 27.3]	−0.023	−0.042, −0.005
Continuous NfL	230	T2	7.9 [5.7, 10.6]	23.9 [17.9, 33]	−0.012	−0.026, 0.001
Continuous NfL	251	T3	25.2 [18.9, 40.6]	25.9 [20, 38.1]	0.004	−0.014, 0.023

Continuous indicate 1 standard deviation increase in log10 transformed WMH or NfL. Adjusted by age, sex, race, education, and APOE4. Beta estimate and (95%CI) is time interaction of WMH or NfL.

associated with cognition only in the first tertile of NfL [median (IQR) 16.5 (13, 18.6)]. For a 1-SD increase in log10 WMH, the rate of cognitive decline was 0.030 units per year (β: −0.030; 95%CI −0.046, −0.014). No association between WMH and cognition was observed in people with higher levels (second and third tertile) of NfL (Table 3A). Across tertiles of WMH, NfL was associated with cognition only in the first tertile of WMH [median (IQR) 2.0 (1.0, 3.0)]. For a 1-SD increase in log10 NfL, the rate of cognitive decline was 0.023 units per year (β: −0.023; 95%CI −0.042, −0.005). No association between NfL and cognition was noted in people with higher levels (second and third tertile) of WMH (Table 3B).

Figure 1 shows the associations of the combined tertiles of NfL and WMH with cognitive decline. Overall, we noted a graded association with increasing levels of

Tertiles of WMH	Tertiles of NfL	n (%)	Median NfL, pg/mL	Median WMH, cc	Beta (95%CI)
T1	T1	113 (16.1)	15.6	1.8	reference
T2	T1	89 (12.7)	16.5	7.5	-0.014 (-0.041, 0.014)
T3	T1	68 (9.7)	17.1	23.9	-0.042 (-0.072, -0.012)
T1	T2	64 (9.1)	24.4	2.3	-0.005 (-0.039, 0.028)
T2	T2	71 (10.1)	25.4	7.6	-0.017 (-0.047, 0.013)
T3	T2	88 (12.6)	25.1	26.1	-0.025 (-0.054, 0.005)
T1	T3	43 (6.1)	40.0	2.0	-0.04 (-0.081, 0.001)
T2	T3	70 (10)	41.4	8.7	-0.041 (-0.075, -0.006)
T3	T3	95 (13.6)	42.9	25.2	-0.027 (-0.059, 0.004)

Figure 1. Association of the combined levels (tertiles) of WMH and NfL with cognitive decline. Adjusted by age, sex, race, education, and APOE4. Beta estimate and (95%CI) is time interaction of the joint WMH and NfL with time.

WMH, particularly in people with lower NfL values. Specifically, compared with people in the first tertile of NfL and WMH (reference group), those in the third tertile of WMH and first tertile of NfL had a faster rate of cognitive decline by 0.042 units per year (β: −0.042; 95%CI −0.072, −0.012). At a higher risk of a rapid cognitive decline were people in the third tertile of NfL and second tertile of WMH when they were compared to people in the first tertile of NfL and WMH (β: −0.041; 95% CI −0.075, −0.006).

We did not find a significant interaction of biomarkers with age, sex, and race in relation to cognitive decline.

Discussion

We prospectively investigated the association of WMH and NfL with cognitive decline to determine whether combining WMH with NfL could provide additional information for cognition in older adults. We found that NfL and WMH were similarly associated with cognitive decline in older people. In addition, our study suggested that in people with lower values (i.e., first tertile) of NfL, WMH may identify individuals with a faster rate of cognitive decline; similar findings for people with lower WMH, where NfL was associated with the rate of cognitive decline. When both biomarkers were combined, we noted a graded association between increasing levels of WMH and the rate of cognitive decline, particularly in people with lower levels of NfL.

Current research methods focus on identifying biomarkers as a tool that may help determine the neurodegenerative disease. In fact, in recent years, biomarkers have gained an increasing significance in the clinical diagnosis of dementia, although, despite the advances, yet not part of the diagnosis.[23] One of the most studied biomarkers of cerebrovascular disease is the WMH volumes. A growing body of research suggests that WMH is associated with cognitive decline and the risk of Alzheimer's disease.[8,9,24] A recent meta-analysis of 36 prospective studies, including 19,040 individuals with an average age of 70 years and 53% women, reported that WMH accounted for a 25% high risk of Alzheimer's disease and 73% risk of vascular dementia.[24] Our findings align with the literature that higher volumes of WMHs are associated with a faster cognitive decline. In comparison to WMH, NfL is more directly related to neurodegenerative diseases since it is located in the cytoplasm of neurons and increased in the blood due to neuron damage. An advantage of NfL is that it could be measured with minimally invasive procedures (e.g., blood draw) readily available and cost-effective.[25] Our findings on NfL and cognitive decline align with several investigations concluding that serum NfL is associated with a faster rate of cognitive decline in older adults.[25–27]

Since most, if not all, of the studies focused on evaluating individual associations of WMH and NfL with cognitive outcomes, including Alzheimer's disease, in our investigation, we aimed to understand whether these biomarkers complement each other in determining the rate of cognitive decline in older adults. Our study addresses two questions: first, if one biomarker is available, does it require the measure of the second biomarker for better assessment of cognitive decline; second, if both biomarkers are available, do they complement each other. We found a similar association of WMH and NfL with the rate of cognitive decline, suggesting similar predictive abilities of biomarkers in relation to cognition. However, we shall acknowledge that their mechanistic pathways differ; while WMH is related to vascular diseases,[28] NfL is a biomarker of neurodegeneration.[29] In addition, we found that within the lower levels of one biomarker (e.g., NfL), the other biomarker (e.g., WMH) may identify people at risk of cognitive impairment since we found a significant association between increasing the levels of biomarker (e.g., WMH volumes) with the rate of cognitive decline. When we combined both biomarkers creating nine categories based on tertiles of WMH and NfL, we found a graded association between increasing levels of WMH and the rate of cognitive decline, suggesting that WMH could be slightly more advantageous than NfL in predicting the rate of cognitive decline in our study population. However, this is the first study that compares NfL with WMH, and therefore, further studies are required to confirm or reject our results.

WMH is clinically interpreted as a surrogate of cerebral small vessel disease. It is attributed to numerous pathophysiological mechanisms, including reduced blood flow (i.e., hypoperfusion), blood–brain barrier dysfunction, and loss of blood vessel volume and integrity.[30] Neurofilament is an axonal cytoskeletal protein found only in neurons, and it is increased in cerebrospinal fluid and serum due to axon damage.[31] While WMH is related to vascular diseases,[28] NfL is more specific to neurodegeneration.[29] In our study, we found that both biomarkers, WMH and NfL, were associated with the rate of cognitive decline; however, we noted a stronger association of WMH with cognition in individuals with lower levels of NfL (i.e., lower tertile). Whether WMH initiates or has an additive contribution to neurodegeneration is a subject of scientific discussion.[28,32] A recent analysis has shown that WMH (i.e., vascular pathologies) has an additive role with Alzheimer's disease-related pathologies in increasing the risk of Alzheimer's.[28,32] Therefore, we may hypothesize that at low levels of NfL, WMH may have a more substantial effect on cognition, but as the NfL levels

increase, there is likely to be a contribution of Alzheimer's disease pathologies that overcomes the more subtle vascular disease effects.

The major strength of our study is its prospective longitudinal design in a population setting. The assessment of cognition after determining levels of biomarkers enabled us to evaluate the rate of decline during the follow-up. Although we did not note race differences in the relationship between biomarkers and cognitive decline, our study is bi-racial (63% African Americans), and our findings were independent of race. In our study, the cognitive assessment was performed on a 3-year cycle enabling us to identify minor differences in cognitive changes. The limitation of the study may include the selection of individuals who underwent the MRI assessment. While we invited everyone with clinical evaluation to be enrolled, participants shall not have medical contraindications (e.g., no heart pacemaker) at the time of the study. Therefore, our results may not apply to all individuals. In addition, specific biomarkers of Alzheimer's disease, such as amyloid PET imaging or CSF biomarkers (e.g., Ab42 and Ab40, t-tau, NfL), were not available in our study, which limits the validation of our results.

In conclusion, both biomarkers, WMH and NfL were similarly associated with the annual rate of cognitive decline in a biracial cohort of adults aged 65 years and older. However, we found that in people with lower levels of NfL, an increase in WMH volumes was associated with a faster rate of cognitive decline in a graded fashion, suggesting that WMH and NfL have different underlying mechanisms affecting cognition.

Author Contributions

Conception and design of the study (AD, CD, KD, PJ, RSW, DAE, and KBR). Acquisition and analysis of data (AD, CD, and KBR). Drafting a significant portion of the manuscript or figures (AD, CD, KD, PJ, RSW, DAE, and KBR).

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Conflict of Interest

None declared.

Data Availability Statement

Deidentified data may be available on request for qualified investigators from https://www.riha.rush.edu/dataportal.html.

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