White Matter Hyperintensity Predicts the Risk of Incident Cognitive Decline in Community Dwelling Elderly

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Abstract.

Background: Unlike western countries, data on white matter hyperintensity (WMH) in community dwelling elderly in Asian population is very limited.

Objective: To examine the relation between baseline WMH burden and the risk of incident cognitive decline in a community-based cohort with Chinese-dwelling elderly.

Methods: We prospectively evaluated the incident cognitive decline for 226 participants in the Shanghai Aging Study. Baseline WMH severity was visually rated by the age-related white matter changes (ARWMC) scale based on MRI. Cox proportional hazards regression model was used to estimate the relative risk (RR) of total ARWMC scale, global ARWMC score, presence of lacune and microbleed, for incident cognitive decline by adjusting potential confounders.

Results: Forty subjects were identified with incident cognitive decline (new onset 34 mild cognitive impairment and 6 dementia) during a median duration of 6 years follow-up. The incidence of cognitive decline was 3.0 (95% confidence interval [CI] 2.2–4.1) per 100 person-years. Increasing total ARWMC scale [RR 1.21 (95%CI 1.06–1.39), \( p = 0.004 \)], confluent WMH [RR 3.16 (95%CI 1.50–6.64), \( p = 0.002 \)], and presence of lacunes [RR 2.73 (95%CI 1.21–6.15)] at baseline were independent predictors of incident cognitive decline.

Conclusion: Our study demonstrated that confluent WMH may increase the risk of incident cognitive decline by 3 folds in community dwelling subjects. Small vessel disease may cause heavy burden of cognitive impairment in the elderly in China.

Keywords: Cognitive decline, dementia, mild cognitive impairment, small vessel disease, white matter hyperintensity

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INTRODUCTION

White matter hyperintensity (WMH), lacunes, and microbleeds observed in MRI are considered various manifestations of arteriolosclerotic small vessel disease and are related to age and vascular risk factors [1]. WMH is almost endemic in western community elderly with prevalence ranging from 50% to 98% [2–6]. Recent studies have shown that WMH is associated with outcomes of cognitive impairment, dementia, urinary incontinence, gait disturbances, depression, and increased risk of stroke and death [7]. There is also evidence for a relationship between WMH and cognitive impairment in demented patients as well as in healthy elderly individuals [8]. Unlike western countries, data on WMH in community dwelling elderly in Asian population is very limited. Longitudinal studies demonstrating that WMH predicts future risks of poor outcomes, including cognitive decline, stroke, functional decline, and mortality are still lacking in this region.

Given that impact of WMH upon cognition may depend on cognitive and brain reserve, and cognitive and brain reserve may vary with ethnicity or culture, it is unknown whether WMH will have similar cognitive impact among Asians as it has upon Caucasians. We previously reported a nearly 40% WMH prevalence in a community-dwelling elderly cohort in Shanghai, and concluded that Han Chinese had a higher prevalence of confluent WMH than white Australians, but a similar prevalence of lacunes and microbleedings, through a population-based cross-national comparison [9]. In this prospective study, we clinically evaluated the incident cognitive decline and estimated its incidence in this community-based cohort followed in the long-term. Additionally, we examined the relation between baseline WMH burden and the risk of incident cognitive decline.

METHODS

Study site and subject recruitment

Subjects in this study were recruited from a part of the Shanghai Aging Study, aiming to investigate the prevalence of mild cognitive impairment (MCI) and dementia among elderly residing in urban Shanghai. Based on the government maintained “registered name list”, we consecutively enrolled subjects focusing on five resident units in the Jing’an Temple Community in urban Shanghai. Potential participants were approached at the door to describe the study. The inclusion criteria of current study were 1) age ≥55 years old; 2) neurologically asymptomatic by comprehensive neurological evaluation; 3) without history of stroke; 4) diagnosed as MCI and normal cognition; and 5) without any contraindications to MRI scanning (pacemakers or other metal objects).

Ethics statement

This study was approved by the Medical Ethics Committee of Fudan University affiliated Huashan Hospital, Fudan University, Shanghai, China. Written informed consent was obtained from all participants and/or their legally acceptable guardians.

Clinical assessment and medical history

From January 1, 2010 through Apr 30, 2010, participants received physical and neurological examinations and MRI scan at Huashan Hospital, Fudan University. Basic demographic data collection included age, sex, and education background. History of diabetes mellitus (DM), hypertension, atrial fibrillation (AF), hyperlipidemia, and coronary artery diseases (CADs) were recorded. DM was defined as type I or II DM treated with antidiabetic therapy. Hypertension was defined as a systolic/diastolic blood pressure of ≥140/90 mm Hg or self-reported hypertension that was being treated with antihypertensive therapy. Participants were considered to have hyperlipidemia based on self-report and if they exhibited any of the following criteria: 1) total cholesterol (TC) level ≥5.9 mmol/l; 2) low-density-lipoprotein cholesterol (LDL-C) level ≥2.6 mmol/l; 3) high-density-lipoprotein cholesterol (HDL-C) level <0.9 mmol/l (male), HDL-C <1.0 mmol/l (female); or 4) triglyceride (TG) level ≥1.8 mmol/l. CADs included stable angina, unstable angina, and myocardial infarction.

Neuropsychological tests

Cognitive function of each participant was tested by a neuropsychological test battery, which covers domains of global cognition, executive function, spatial construction function, memory, language, and attention. The battery contained: 1) Mini Mental State Examination (MMSE); 2) Conflicting Instructions Task (Go/No Go Task); 3) Stick Test; 4) Modified Common Objects Sorting Test; 5) Auditory Verbal Learning Test; 6) Modified Fuld Object Memory
Evaluation; 7) Trail-making test A&B; and 8) RMB (Chinese currency) test. The neuropsychological tests were administered by study psychometrists according to the education level of each participant. All tests were conducted in Chinese within 90 min. Normative data and detail description of these tests were reported elsewhere [10, 11].

Consensus diagnoses for cognitive function

Study neurologists and neuropsychologists reviewed the functional, medical, neurologic, psychiatric, and neuropsychological data and reached a consensus regarding the presence or absence of dementia using DSM-IV criteria [12]. Only those who were not diagnosed with dementia were considered for a diagnosis of MCI, which was defined according to Petersen’s criteria [13–15].

MRI Acquisition and image analysis

All MRI examinations were performed on a 1.5 T Scanner (GE) with 3D T1-weighed, T2-weighed, axial FLAIR, and gradient recall echo sequences: T1-weighed \( [\text{repetition time (TR)/echo time (TE) = 25/2.3 ms, flip angle = 30 degrees, field of view = 230 mm, slice thickness/gap = 5/0.5 mm}] \), T2-weighed \( [\text{TR/TE} = 3000/80 ms, turbo factor = 18, field of view = 230 mm, slice thickness/gap = 5/0.5 mm]} \), T2-weighed \( [\text{TR/TE} = 11 000/125 ms, field of view = 230 mm, slice thickness/gap = 5/0.5 mm, time interval = 2800 ms}, \) and gradient recall echo (GRE) \( [\text{TR/TE} = 350/30 ms, flip angle = 30 degrees, field of view = 230 mm, slice thickness/gap = 5/0.5 mm}] \).

We defined WMH, lacunes and microbleeds according to the STRIVE (STandards for Reporting Vascular changes on Neuroimaging) [16]: WMH was hyperintense on T2-weighted and FLAIR, and hypointense and either hypointense or isotense on T1-weighted sequences. WMH severity was visually rated by the age-related white matter changes (ARWMC) scale [8]. The “total ARWMC scale” is the sum of score for each of the five anatomical regions (frontal, parietal-occipital, temporal, infratentorial, basal ganglia) in both hemispheres, which ranges from 0 to 30 totally for ten regions. The “global ARWMC score” (range 0–3) is the ARWMC score of the most severe WMC region among ten regions, with score 0, 1, 2, and 3 representing no, focal lesion, early confluent, and confluent lesions, respectively. The “global ARWMC score” significantly correlates with the “total ARWMC scale” \( p < 0.001 \) [17]. Lacune was defined as well-defined hypointensity with diameter 3–15 mm on T1-weighed images, hyperintensity on T2-weighed images, and hypointensity surrounded by bright-rim on FLAIR. We defined microbleed as a circular area of marked and homogeneous signal loss on gradient recall echo T2-weighed MRI, of size ranges from 2–10 mm, that was not located in sulcal areas to avoid confusion with flow void from cerebral vessels. The following intra-rater reliability was obtained by re-rating 20 randomly selected MRI scans: intra-class correlation for total ARWMC scale: 0.92 (95% CI: 0.82–0.97), number of lacune: 0.87 (95% CI: 0.72–0.95), number of microbleed: 0.94 (95% CI: 0.85–0.98), kappa for presence of lacune: 0.66 and microbleed: 1 [9].

APOE genotype assessment

DNA of each participant was extracted from blood or saliva samples. APOE polymorphisms (rs429358 and rs7412) were assayed using the TaqmanSNP genotyping method [18]. The presence of at least one \( e4 \) allele was treated as being APOE \( e4 \) positive.

Follow-up procedure

From April 1, 2014 to October 31, 2016, we conducted a follow-up study for this cohort. A research coordinator contacted all the participants based on their contact information recorded at the baseline examination. Individuals were considered lost-to-follow up if they: 1) were deceased; 2) could not be contacted; 3) refused to be interviewed; or 4) were suffering with severe mental disorder, impairment of vision, hearing or speaking and were not able to cooperate with clinical interview and neuropsychological tests.

Participants were firstly asked for their cognitive complaints, which they, their proxy, or a nurse or physician indicated that they had problems with memory or thinking. Cognitive function of participants was evaluated by using the neuropsychological batteries which were used at the baseline. Consensus diagnosis was conducted by the same neurologists and neuropsychologists by using the same diagnoses criteria at the baseline. Cognitive decline was defined as incident dementia (normal progressed to dementia, and MCI progressed to dementia) or incident MCI (normal progressed to MCI).
**Statistical analysis**

"Total ARWMC scale" was categorized into quartiles. "Global ARWMC score" was categorized into 3 severity rating: 0, 1, and ≥2, representing no, focal lesion, and confluent lesions, respectively. The incidence rate of cognitive decline was estimated as the number of incident dementia and MCI cases occurring during the follow-up period divided by the cumulative follow-up period of all study subjects and described as “per 100 person-years” with 95% confidence intervals (CIs).

The Student t-test was used to compare continuous variables. The Chi-square test or Kruskal-Wallis test was used for comparing categorical variables. Univariable Cox proportional hazards regression model (model 1) was used to estimate the relative risk (RR) with 95% CIs of “total ARWMC scale”, “global ARWMC score”, presence of “lacune” or “microbleed”, for incident cognitive decline. Multivariable Cox proportional hazard regression models with stepwise selection were used to detect the right independent risk factors of “total ARWMC scale”, “global ARWMC score”, presence of “lacune” and “microbleed”, and estimate the RR with 95% CIs. Potential confounders in the models included age, sex, and education years (model 2), and age, sex, education, baseline MMSE score, history of hypertension, DM, hyperlipidemia, AF, CAD, and APOE ε4 (model 3). Kaplan–Meier curves were used to present the estimated cumulative conversion rates to cognitive decline by follow-up time in different WMH subgroups. The log-rank test was used to compare cumulative hazard of cognitive decline estimates within different subgroups.

All p-values and 95%CI were estimated in a two-tailed fashion. Differences were considered to be statistically significant at p < 0.05. Data were analyzed using SPSS 16.0 (SPSS Inc., IL, USA).

**RESULTS**

According to the inclusion criteria of this study, 278 participants (246 with normal cognition and 32 with MCI at the baseline) were determined as the eligible study subjects. Table 1 shows the demographic and clinical characteristics of study subjects at baseline and follow-up. Among the 278 eligible subjects enrolled at the baseline, 52 were lost-to-follow up (19%). Reasons for lost-to-follow up were deceased (n = 19), refusal (n = 8), and lost contact (n = 35). No significant differences were found for baseline characteristics between those who were followed and those lost to follow-up.

Comparing the baseline characteristics between 40 subjects with cognitive decline and 186 with cognitive stable, those with cognitive decline were

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**Table 1**

Demographic, clinical, and neuroimaging data of study subjects at the baseline

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Eligible subjects</th>
<th>Lost–to–follow up</th>
<th>Followed up n = 226</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± sd</td>
<td>68.6 ± 6.0</td>
<td>68.7 ± 6.9</td>
<td>72.2 ± 5.8</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>130 (46.8)</td>
<td>25 (48.1)</td>
<td>19 (47.5)</td>
</tr>
<tr>
<td>Education years, mean ± sd</td>
<td>11.6 ± 3.8</td>
<td>11.2 ± 4.6</td>
<td>9.5 ± 4.2</td>
</tr>
<tr>
<td>MMSE, mean ± sd</td>
<td>28.5 ± 1.8</td>
<td>28.6 ± 1.8</td>
<td>27.3 ± 2.7</td>
</tr>
<tr>
<td>Normal cognition, n (%)</td>
<td>246 (88.5)</td>
<td>46 (88.5)</td>
<td>35 (87.5)</td>
</tr>
<tr>
<td>Mild cognitive impairment, n (%)</td>
<td>32 (11.5)</td>
<td>6 (11.5)</td>
<td>5 (12.5)</td>
</tr>
<tr>
<td>APOE ε4+, n (%)</td>
<td>41 (14.7)</td>
<td>8 (15.4)</td>
<td>8 (20.0)</td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td>145 (52.2)</td>
<td>30 (57.7)</td>
<td>24 (60.0)</td>
</tr>
<tr>
<td>History of DM, n (%)</td>
<td>37 (13.3)</td>
<td>8 (15.4)</td>
<td>9 (22.5)</td>
</tr>
<tr>
<td>History of hyperlipidemia, n (%)</td>
<td>96 (34.5)</td>
<td>13 (25.0)</td>
<td>17 (42.5)</td>
</tr>
<tr>
<td>History of AF, n (%)</td>
<td>7 (2.5)</td>
<td>1 (1.9)</td>
<td>2 (5.0)</td>
</tr>
<tr>
<td>History of CAD, n (%)</td>
<td>27 (9.7)</td>
<td>4 (7.7)</td>
<td>7 (17.5)</td>
</tr>
<tr>
<td>Total ARWMC scale, median (min, max)</td>
<td>3 (0.17)</td>
<td>4 (0.17)</td>
<td>5 (0.10)</td>
</tr>
</tbody>
</table>

MMSE, Mini-Mental State Examination; CAD, coronary heart disease; DM, diabetes mellitus; AF, atrial fibrillation; ARWMC, age-related white matter changes; *cognitive decline versus cognitive stable.
We identified 40 subjects with incident cognitive decline (new onset 34 MCI and 6 dementia) during a median follow-up duration of 6 years. The incidence of cognitive decline was 3.0 (95%CI 2.2–4.1) per 100 person–years. We report the incidence of cognitive decline among all followed subjects and in different subgroups in Table 2. Cognitive decline incidence and RRs increased by the enhancement “total ARWMC scales” and “global ARWMC score”, and the presence of lacunes and microbleeds. The risk of cognitive decline for subjects with the highest quartile (5–13) of “total ARWMC scales” was 5 times [RR 5.02 (95%CI 1.71–14.75)] of that of those with the lowest quartile (0–1). The risk of cognitive decline for subjects with confluent lesions was 3.7 times [RR 3.70 (1.33–10.83)] of those without any lesion. Kaplan–Meier curves indicated that, the cumulative hazard of the incident cognitive decline of subjects with confluent lesions increased more dramatically, second with that of subjects with focal lesions, than that of subjects without any lesion, by follow–up time (Log–rank test p < 0.001) (Fig. 1).

Results of univariable (model 1) and multivariable (model 2 and 3) Cox regression models are shown in Table 3. Adjusted for age, sex, and education years (model 2), increasing “total ARWMC scale” [RR 1.23 (95%CI 1.09–1.39), p = 0.001], and confluent WMH [RR 4.05 (95%CI 2.03–8.08), p < 0.001], were found as independent predictors of incident cognitive decline. After adjusting for age, sex, education, baseline MMSE score, history of hypertension, DM, hyperlipidemia, AF, CAD, and APOE e4 (model 3), increasing “total ARWMC scale” [RR 1.21 (95%CI 1.06–1.39), p = 0.004], confluent WMH [RR 3.16 (95%CI 1.50–6.64), p = 0.002], and presence of lacunes [RR 2.73 (95%CI 1.21–6.15)] were found as independent predictors for incident cognitive decline (Table 3).
**DISCUSSION**

In this prospective study, we clinically evaluated the incident cognitive decline and estimated its incidence as 3.0 (95% CI 2.2–4.1) per 100 person-years, in this community-based cohort followed averagely 6 years. Increasing "total ARWMC scale", confluent WMH, and presence of lacunes were independent predictors for incident cognitive decline. To our knowledge, this is the first longitudinal study investigating incidence of cognitive decline in relation to severity level of WMH, and estimating the relative risk of cognitive impairment due to WMH in a community-based sample in Chinese or Asian population. Our results were consistent with that of previous studies in western populations.

Early in 2001, the Rotterdam Scan Study reported that, of 1077 subjects (60–90 years) who underwent 1.5T MR scanning, 8% were completely free of subcortical white matter lesions, 20% had no periventricular white matter lesions, and 5% had no white matter lesions in either subcortical or periventricular locations [19]. The prevalence data were very limited in Asian population. In our previous study of a population-based cross-national comparison, we found that confluent WMH were significantly more prevalent in Han Chinese (38.5%) than White Australians (28.4%; p = 0.01), but had a similar prevalence of lacunes and microbleeds. Comparing to White Australians, Chinese ethnicity was associated with confluent WMH (OR 1.7, 95% CI 1.1–2.6, p = 0.01) [9].

Establishing a temporal relationship between cerebral small vessel disease and cognitive decline in the general population may provide evidence for a causal role of cerebral small vessel disease in the etiology of dementia. However, most evidence was derived from western worlds. The Cardiovascular Health Study reported that a five-point or greater decline in cognitive scores over up to 3 years was more often observed for participants with WMH (OR 1.2, 95% CI 0.98–1.47) [20]. De Groot et al. examined the relation between severity of WMH and cognitive decline over a mean follow-up period of 7.3 years in 563 elderly subjects sampled from the general non-demented Dutch population. Subjects with severe periventricular WMH experienced cognitive decline nearly three times as fast (0.28 MMSE points/year [95% CI 0.20–0.36]) as the average (0.10 points/year [95% CI 0.09–0.11]), after adjusting for age, sex, educational level, measures of depression, and brain atrophy and infarcts [21]. The population-based Rotterdam Scan Study prospectively followed 1,015 participants, who were 60 to 90 years of age and free of dementia and stroke at baseline. During 3,697 person-years of follow-up, it was found that a greater severity of periventricular WMH was significantly associated with an increased risk of dementia (hazard ratio [HR] 1.59, 95% CI 1.13–2.25), adjusted for age, sex, and education level [22]. Later on, this study reported that periventricular WMH, brain infarcts, and generalized brain atrophy on MRI were associated with the rate of decline in cognitive function. Increasing periventricular hyperintensities only predicted a higher rate of annual decline in MMSE scores. These structural brain changes on MRI, which are thought to be caused by small vessel disease, were specifically associated with decline in information processing speed and executive function [23]. Smith et al. prospectively followed 67 community volunteer subjects with normal cognition for incident cognitive decline for averagely 6 years. The study found that high WMH was a predictor of progression from normal to MCI (adjusted HR 3.50; 95% CI 1.33–8.17; p = 0.01) [24].

Forty-nine subjects in the Oregon Brain Aging Study...
were followed via at least three brain MRIs and annual cognitive and neurologic assessments until diagnosed with persistent cognitive impairment. The study not only found that greater baseline periventricular WMH (HR 1.06, 95% CI 1.01–1.10, \( p = 0.02 \)) conferred a higher risk of cognitive impairment, but also found that increased progression of periventricular WMH volume (HR 1.94, 95% CI 1.3–3.1, \( p = 0.001 \)) conferred higher risk of persistent cognitive impairment [25]. The Framingham Offspring Study reported that, in a large community-based sample of middle-aged adults, WMH volume (HR 2.22, 95% CI 1.32–3.72), extensive WMH volume (HR 3.97, 95% CI 1.10–14.30), and brain infarct (HR 6.12, 95% CI 1.82–20.54) were associated with an increased risk of dementia, independently of vascular risk factors and interim stroke. WMH volume (OR 2.47, 95% CI 1.31–4.66) and extensive WMH volume (OR 1.49, 95% CI 1.14–1.97) were associated with incident amnestic mild cognitive impairment in participants aged \( \geq 60 \) years only [26].

Various potential mechanisms may underlie the association of WMH with the risk of cognitive decline. Further progression of small vessel disease may cause interruption of frontosubcortical circuits and/or secondary cortical atrophy [27, 28]. WMH may interact with typical Alzheimer’s disease pathology, such as amyloid plaques and neurofibrillary tangles [29]. Amyloid angiopathy or Wallerian degeneration may result to cortical atrophy [30].

The advantages of this study included the prospective design of a population-based study sample with high rate of a 6-year follow-up. Comprehensive clinical and neuropsychological, and genetic data were collected for investigation. There are certain limitations in our study. First, those lost-to-follow-up subjects had higher total ARWMC scale and more had confluent WMH, comparing with subjects recruited at the baseline. This attrition is likely to have resulted in underestimation of the association between WMH and the risk of cognitive decline. This should be taken into account when generalizing our results to the general population. Second, cognitive decline of subjects in this study didn’t show difference until the 5th year of follow-up, because there was only one visit during the follow-up of 6 years. Thus, a bias of the time of cognitive decline could not be avoided. Third, analyses stratified by APOE \( \varepsilon 4 \) status could be more of assistance than just adjustment in understanding vascular neurodegenerative interactions. However, only 8 subjects with APOE \( \varepsilon 4 + \) developed to “cognitive decline” during the follow-up. Such a small sample size may influence the goodness-of-fit of the Cox regression model being used for the statistical analysis. Fourth, regional ARWMC may give more information on the regional difference on cognitive decline. In our study, however, we did not find the significant risk difference of the certain anatomical region(s) and the severity due to the relatively small sample size. Fifth, we combined incident dementia and MCI as the end point of “cognitive decline”. However, progressions from normal to MCI, from normal to dementia, and from MCI to dementia may be different. Recruitment and follow-up of subjects with larger sample size may help to separately elucidate different progressions in further studies. Sixth, lacking of longitudinal data of MRI image is another shortcoming in our study. The baseline WMH severity might not be sufficient to reflect the progression trends of small vessel disease and might not be the better predictor of persistent cognitive decline. Additionally, volumetric abnormalities of the brain may be predictive of an increased risk of progressively impaired cognition. However, brain measures such as hippocampal or total brain volume were not analyzed in this study. Further studies are needed to elaborate these measures. Lastly, the information from this study is valuable as data of WMH on Asian population is limited. Since the analysis only utilize a small community data, some of the conclusion is a bit of overstatement.

Our study demonstrated that confluent WMH may increase the risk of incident cognitive decline by 3 folds. Small vessel disease may cause heavy burden of late-life cognitive impairment in the elderly in China. Therefore, further longitudinal studies with larger sample size should observe the progression of structural changes of MRI, and its correlation with the development of cognitive impairment.

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