Cerebral White Matter Lesions and Cognitive Function in a Non-demented Chinese Veteran Cohort

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This study examined the association between cerebral white matter lesions (WMLs) and cognitive function in a male, non-demented Chinese veteran cohort. A total of 662 participants underwent CT scan and cognitive function assessments; 51 were excluded from the analysis because they exhibited non-lacunar infarcts or suspected dementia. Subjects were allocated to one of four groups according to WML status and between-group comparisons were made for seven cognitive function tests. Logistic regression was used to assess odds ratios for impaired performance associated with WML status. In all cognitive tests, subjects with severe WMLs differed significantly from those without WMLs or with mild WMLs, and in three tests subjects with severe WMLs differed significantly from those with moderate WMLs. For each cognitive test severe WMLs were strongly associated with increased risk of impaired performance. Severe WMLs were associated with greater diminished cognitive function and there may be a WML threshold after which, in elderly Chinese subjects, an impact on cognitive function occurs.

KEY WORDS: CEREBRAL WHITE MATTER LESIONS; COGNITIVE IMPAIRMENT; ELDERLY; CHINESE

Introduction

Cerebral white matter lesions (WMLs) as a marker of small vessel disease in the brain are commonly found in the elderly presumed to be free of neurological disease and they are known to increase in frequency with age.¹ - ³ On computed tomography (CT) scans, WMLs appear as areas of patchy low attenuation, distributed in the periventricular and/or subcortical regions. The corresponding lesions appear as areas of hyperintensity on T2-weighted magnetic resonance imaging (MRI). Several studies have evaluated cognitive changes in non-demented elderly with WMLs and have generally found a correlation between cognitive impairment and WMLs.² - ⁵

Cerebrovascular disease (CVD) is highly prevalent in China and is a heavy social and economic burden in the ageing population.⁶,⁷ Cognitive impairment in elderly Chinese individuals seldom attracts the attention of family members and clinicians, even in the elderly with priority medical services. Chinese elderly are not accustomed to talking about ‘intelligence decline’ with clinicians; it is
generally felt that cognitive problems are a normal consequence of ageing and are less important compared with other symptoms that result from CVD, such as impaired motor function, gait abnormality and dysphasia.

The cohort for the study reported here comprised retired male veterans with free medical care, similar social and educational backgrounds, and lifestyle. This special ageing population provided an excellent opportunity to evaluate cognitive function in the Chinese elderly. The high sensitivity of MRI has increasingly replaced CT for delineating WMLs, however CT is less costly and more easily performed than MRI, which is a particular consideration in mainland China. Wahlund et al.\(^8\) showed that large WMLs were detected equally well with both CT and MRI. Moreover, previous research has suggested that only large WMLs are linked to higher vascular risk and had clinical significance.\(^3,4\) Thus, in the current study, CT was used to detect WMLs and the relationship between WMLs and cognitive performance in male non-demented Chinese elderly was evaluated.

Subjects and methods

**SUBJECTS**

Participants were recruited from the Cognitive Disorders of High Rank Retired Military Officers in Nanjing Study, an ongoing, prospective study aimed at identifying cognitive disorders and their risk factors. The cohort comprised 35 veteran convalescent camps in Nanjing, China, catering for 5900 retired male military officers of high rank. Each camp had nurses and clinicians who cared for the elderly and liaised with doctors at Jinling Hospital, Nanjing University School of Medicine, where necessary. All the elderly had the privilege of receiving entirely free medical examinations and treatment, as well as hospitalization in Jinling Hospital. They were given an overall physical examination once per year, for which 50% were hospitalized.

Potential participants were informed that the study would investigate cognitive function for the early detection of dementia and voluntarily registered their interest to participate. The study was approved by the Medical Ethics Committee of Jinling Hospital. All participants gave written informed consent. At the evaluation, clinical information and demographic data were collected. Those subjects recruited were in relatively good health. Subjects were excluded if they had a history of neurodegenerative or major psychotic disorders, a history of stroke or transient ischaemic attacks, were taking medications with potentially potent central nervous system effects (e.g. sedatives, antipsychotics), had considerable hearing or sight disabilities, or other medical illness that could affect measurement of their cognitive function.

**THE CT SCAN PROCEDURE**

A non-contrast CT scan (10 mm slice thickness at 10 mm intervals) was performed. WMLs were defined as focal or diffuse hypodensities (\(\geq 5 \text{ mm}\)) in the periventricular or deep white matter, not involving the cortex, with ill-defined margins to differentiate them from infarction.\(^8,9\) They were graded on a four-point scale according to the method of Wahlund et al.\(^8\) and subjects were divided into four groups: without WMLs (grade 0); mild WMLs (grade 1); moderate WMLs (grade 2); and severe WMLs (grade 3). Silent lacunar infarction was defined as a low-density area (well-defined areas of \(\geq 3 \text{ mm to } \leq 15 \text{ mm}\)) on CT but without a history of stroke, as determined from the patient, their family or other accessible information. An experienced neuroradiologist, blinded to the cognitive data, read the scans.
MEASUREMENTS OF COGNITIVE FUNCTION
Trained examiners carried out the following cognitive tests in a quiet room.

Delayed word recall test
This test was used to assess verbal memory using a selected word list of 10 common nouns (each noun comprised two Chinese words). The list was visually presented and subjects were asked to read and learn it twice slowly. There was then a delay of 5 min before they were asked to recall the words on the list, during which time another test was given. Test scores ranged from 0 to 10 words recalled.

Animal category fluency test
This was conducted as a brief test to examine executive function. Subjects were asked to name as many animals as possible within 1 min. The test score was the total number of animals named.

Symbol digit modalities test
This test alters the format of the digit symbol subtest of the Wechsler Adult Intelligence Scale–Revised (WAIS–R) and is designed to measure psychomotor speed and concentration. Subjects were required to translate the numbers 1 – 9 into symbols within 90 s. The test score was the total number of correct translations to symbols within the set time.

Trail making test (part A)
This test is well-known for its ability to examine speed and attentiveness. Using a pencil, subjects were asked to connect 25 encircled numbers, randomly arranged on a page, into numerical order. The test score was the time taken to complete the test.

Block design test
Visuospatial and constructive skills were assessed using the Block design test. The subject was presented with red and white blocks and was asked to construct replicas of designs printed in smaller scale. The score was calculated according to the WAIS–R block design subtest.

Digit span test
This test was carried out to assess short-term and working memory. It consists of two parts: repeating forward digit sequences and also repeating digit sequences in reverse order. The longest sequences of digits correctly repeated in the forward and reverse order were recorded.

Clock drawing test
This is a quick and useful test for assessing visuospatial, constructional and executive function. The subjects were asked to draw a clock and set the hands and numbers on the face at 01:45. A 10-point scoring system was used.

STATISTICAL ANALYSIS
Subjects were divided into four groups defined by their WML status (without, mild, moderate and severe). Analysis of variance was used to compare demographic continuous variables and the $\chi^2$-test was used to compare categorical data. Multivariate analysis of covariance, adjusting for age, was used to compare cognitive performance of the four WML status groups. Logistic regression adjusted for age was used to assess odds ratios (ORs) and 95% confidence intervals (CIs) for impaired performance associated with WML status. Cognitive function was dichotomized into impairment (cognitive test score $\leq 1.5$ SD from the cohort mean) and favourable function (cognitive test score $> 1.5$ SD from the cohort mean). The ORs and 95% CIs for impaired performance associated with
WMLs were analysed using logistic regression. For categorical variables, the group without WMLs was set as an indicator to assess the ORs of the other three WML status groups. All statistical evaluations were carried out using the Statistical Package for Social Sciences (SPSS® version 10.0; SPSS Inc., Chicago, IL, USA) and \( P < 0.05 \) was considered to be statistically significant.

**Results**

A total of 662 participants underwent cerebral CT and cognitive evaluation. Of these, 26 showed non-lacunar infarction on CT (cortical infarcts, cerebellar infarcts, brainstem infarcts and other infarcts >15 mm) and 25 were suspected of having dementia; these subjects were all excluded thus resulting in a study population of 611 elderly participants. The CT and cognitive function assessments were performed within 1 month for 85% of participants and within 3 months for all.

Age and educational levels of the groups categorized by WML status are shown in Table 1; there were no significant differences in education level, however the groups with WMLs were significantly older than those without WMLs and the groups with WMLs also differed significantly from each other.

Raw scores of cognitive performance for each group, categorized by WMLs status and the respective \( P \)-values for the multivariate analyses of covariance are shown in Table 2. Since there were no significant differences in education level between the groups it was only necessary to adjust for age in the multivariate analysis of covariance. In all tests, cognitive performance in individuals with severe WMLs differed significantly from performances in individuals without and with mild WMLs. Cognitive performance in individuals with severe WMLs also differed significantly from performance in individuals with moderate WMLs in the trail making A, symbol digit modalities and digit span tests. Subjects with moderate WMLs showed significant differences in five cognitive tests compared with those without WMLs (digit span, animal category fluency, block design, clock drawing and delayed recall tests) and in three cognitive tests compared with those with mild WMLs (digit span, block design and clock drawing tests).

The cut off points to define impaired performance for each cognitive test were: trail making A \( \geq 102 \); symbol digit modalities \( \leq 18 \); digit spans \( \leq 7 \); animal category fluency \( \leq 8 \); block design \( \leq 13 \); clock drawing \( \leq 5 \); delayed recall \( \leq 3 \). Analysis of

<table>
<thead>
<tr>
<th>Without WMLs (grade 0) (( n = 196 ))</th>
<th>Mild WMLs (grade 1) (( n = 201 ))</th>
<th>Moderate WMLs (grade 2) (( n = 141 ))</th>
<th>Severe WMLs (grade 3) (( n = 73 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 77.8 ± 2.4</td>
<td>78.6 ± 2.6(^c)</td>
<td>79.9 ± 2.9(^a)</td>
<td>80.7 ± 2.8(^{a,b})</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 5 years 136 (69.4)</td>
<td>141 (70.1)</td>
<td>97 (68.8)</td>
<td>55 (75.3)</td>
</tr>
<tr>
<td>&lt; 5 years 60 (30.6)</td>
<td>60 (29.9)</td>
<td>44 (31.2)</td>
<td>18 (24.7)</td>
</tr>
</tbody>
</table>

Data are mean ± SD or number (%). One-way analysis of variance between-group comparisons: \(^aP < 0.001\) versus without WMLs and mild WMLs; \(^bP < 0.05\) versus moderate WMLs; \(^cP < 0.01\) versus without WMLs.
results showed that, after adjusting for age, severe WMLs were strongly associated with impaired performance in each of the cognitive tests relative to without WMLs. Moderate WMLs were associated with a significantly increased risk of impaired performance in the digit span and clock drawing tests (Table 3).

Discussion

Our study is a large investigation into the relationship between CT detected WMLs and cognitive function in an elderly non-demented cohort in China. This specific, elderly male group, with similar socioeconomic backgrounds and a narrow age range, provided a good opportunity to perform cognitive studies. Education has been shown to influence the relationship between WMLs and cognition and, since the demographic data in the present study showed no significant differences in WML
status with education level, the confounding factor of education could, therefore, be ignored. Age is a strong predictor of WMLs, an important risk factor for cognitive defects and may accelerate the appearance of all types of dementias.\textsuperscript{2,4} Although the age range of our subjects was narrow, the mean ages of the groups differed significantly, hence age was used as a covariant in comparing the cognitive tests of the groups. To avoid over adjustment, cerebrovascular risk factors (e.g. hypertension and diabetes), that are considered to be part of the causal chain in the development of WMLs, were not adjusted for in this study.

A clear distinction in cognitive performances between the groups was shown. Individuals with severe WMLs performed worst in all the cognitive tests. The second worst performances were from individuals with moderate WMLs. Subjects with mild WMLs showed no significant differences in performance compared with subjects without WMLs. In a further attempt to demonstrate a clinical relationship, the ORs for impaired performances in the different WML status groups were examined. Severe WMLs had the strongest association with cognitive impairment in all of the cognitive tests relative to the without WMLs group. The moderate WMLs group demonstrated significant relationships with impairment in two cognitive tests (digit span and clock drawing).

Previous research from the Framingham Heart Study showed that only large WMLs were linked to higher vascular risk and had clinical significance among those without neurological disease.\textsuperscript{1–3} Since MRI is thought to be superior to CT in the detection of WML,

### TABLE 3:
Odds ratios and 95% confidence intervals for impaired cognitive performance in elderly non-demented Chinese individuals examined by computed tomography for the presence of white matter lesions (WMLs) ($n = 415$) compared with subjects without WMLs ($n = 196$)

<table>
<thead>
<tr>
<th>Cognitive function test</th>
<th>Mild WMLs (grade 1) ($n = 201$)</th>
<th>Moderate WMLs (grade 2) ($n = 141$)</th>
<th>Severe WMLs (grade 3) ($n = 73$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trail making A</td>
<td>0.81 (0.38, 1.71)</td>
<td>1.83 (0.87, 3.87)</td>
<td>3.03 (1.33, 6.95)</td>
</tr>
<tr>
<td>NS</td>
<td>NS</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Symbol digit modalities</td>
<td>1.55 (0.66, 3.63)</td>
<td>1.65 (0.66, 4.15)</td>
<td>3.67 (1.44, 9.34)</td>
</tr>
<tr>
<td>NS</td>
<td>NS</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Digit span</td>
<td>2.08 (0.86, 5.00)</td>
<td>3.73 (1.51, 9.27)</td>
<td>10.22 (4.01, 26.03)</td>
</tr>
<tr>
<td>NS</td>
<td>&lt; 0.01</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Animal category fluency</td>
<td>1.21 (0.52, 2.79)</td>
<td>2.21 (0.93, 5.23)</td>
<td>4.62 (1.82, 11.73)</td>
</tr>
<tr>
<td>NS</td>
<td>NS</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Block design</td>
<td>1.19 (0.54, 2.65)</td>
<td>2.04 (0.89, 4.69)</td>
<td>3.69 (1.49, 9.08)</td>
</tr>
<tr>
<td>NS</td>
<td>NS</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Clock drawing</td>
<td>1.35 (0.52, 3.53)</td>
<td>4.27 (1.71, 10.63)</td>
<td>7.99 (2.94, 21.77)</td>
</tr>
<tr>
<td>NS</td>
<td>&lt; 0.01</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Delayed recall</td>
<td>1.17 (0.61, 2.27)</td>
<td>1.98 (0.98, 3.99)</td>
<td>2.84 (1.29, 6.24)</td>
</tr>
<tr>
<td>NS</td>
<td>NS</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
</tbody>
</table>

Data are odds ratio (95% confidence intervals) and $P$-value. Logistic regression was adjusted for age. Impaired cognitive performance is a cognitive test score $\leq 1.5$ SD from the cohort mean. NS, not significant ($P > 0.05$).
the WMLs detected in our study by CT are likely to be more severe and, therefore, more likely to exert an effect on cognition. The cognitive effects of WMLs may result from the disruption of white matter pathways connecting functionally related cortical and subcortical structures. Previous studies have shown that abnormalities in frontal lobe metabolism may underlie cognitive deficits in subjects with WMLs. Much research has suggested that WMLs result in poorer performance in executive functioning, particularly among subjects who are not demented, and a correlation between WMLs and attention as well as working memory has been shown. Other studies, however, have reported no relationship between WMLs and performance in verbal fluency and the Stroop effect. Nordahl et al. reported that subjects with mild cognitive impairment and WMLs were impaired not only in episodic memory tasks, but also in a battery of working memory tasks in both verbal and spatial domains, as well as in attention control, suggesting that episodic memory failure is secondary to general impairment in executive function.

Our results showed that, as the WMLs of individuals became more severe, significant test differences were found in more cognitive domains compared with those without or with mild WMLs, finally involving all cognitive domains. This indicates that a threshold level of WMLs may be needed to impact on different cognitive functions. Cognitive impairment found in some cognitive tests but not others could be related to a primary influence of WMLs, or secondary to deficits in the executive control processes that impact on a wide range of cognitive domains.

So far, the cause of WMLs remains a matter of debate. It is thought that they result from arteriosclerosis of the small penetrating arteries and arterioles supplying the white matter. These vascular alterations ultimately impair autoregulatory adaptation to changes in cerebral blood flow and result in diffuse areas of WMLs. CVD is commonly found in the elderly in China. Considerable evidence has shown that CVD can cause dementia in the absence of Alzheimer’s disease pathology and also may accelerate cognitive decline in subjects with Alzheimer’s disease. In contrast to refined morphological criteria for Alzheimer’s disease and other degenerative dementias, vascular cognitive syndromes represent a heterogeneous group of disorders and the exact role of CVD for cognitive decline remains controversial.

Where WMLs are the main vascular aetiology they comprise a homogeneous subtype of subcortical ischaemic damage and provide a good vehicle with which to investigate cognitive deficits caused by vascular pathology. They account for an important number of cases of dementia and vascular cognitive impairment, and are major contributors to cognitive impairment in elderly people. We postulate that WMLs, particularly those categorized as large, contribute to cognitive impairment in elderly Chinese people. Individuals with WMLs are at risk of dementia and some, but not all, progress to dementia. Future studies on our cohort may help to clarify the impact of WMLs on the likelihood of progression from cognitive impairment to dementia.

Conflicts of interest
No conflicts of interest were declared in relation to this article.

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