Association of White Matter Integrity and Cognitive Functions in Patients With Subcortical Silent Lacunar Infarcts

Yaojing Chen, BS; Ailin Wang, BS; Jinfu Tang, PhD; Dongfeng Wei, MD; Peng Li, MD; Kewei Chen, PhD; Yongyan Wang, BS; Zhanjun Zhang, MD

Background and Purpose—Silent lacunar infarct (SLI) is a risk factor for dementia. This study investigated the white matter integrity abnormality and its relationship to the cognition impairments in SLI patients.

Methods—Between 27 patients with SLI in basal ganglia and 30 healthy controls, we assessed the difference in a battery of neuropsychological tests and in white matter integrity measurements, fractional anisotropy, and mean diffusivity, using tract-based spatial statistics.

Results—Compared with healthy controls, SLI patients performed worse in general mental status, memory, executive function, and language ability. They also had reduced fractional anisotropy and increase mean diffusivity in brain regions such as the body and genu of corpus callosum, the forceps minor, the bilateral superior and bilateral anterior corona radiate, and the left external capsule. Furthermore, we found that in SLI patients, fractional anisotropy measure in left external capsule was positively correlated to the performance in memory and language ability.

Conclusions—SLI in basal ganglia leads to local and remote white matter integrity damages and to the cognition impairments. (Stroke. 2015;46:00-00. DOI: 10.1161/STROKEAHA.115.008998.)

Key Words: cognition ▪ diffusion tensor imaging ▪ subcortical infarction

Silent lacunar infarct (SLI) is a type of silent stroke that results from occlusion of one of the penetrating arteries providing blood to the brain’s deep structures. Reviewed previously, its prevalence is >20% in healthy elderly individuals. SLI has not received enough attention, yet because it usually elicits no clinical symptoms. However, SLI is associated with deficits in cognitive functions, such as impairments in perceptual speed, semantics and episodic memory, and increased risk of dementia.

The mechanism of cognition injury in SLI has not been studied sufficiently and is not well understood. Some studies suggest that microvascular injury may be the leading cause for cognitive impairments in SLI. However, a recent study did not find damaged cerebrovascular reactivity measured with blood-oxygen-level dependent functional magnetic resonance imaging at 7 T in patients with lacunar infarcts.

Growing evidence points to the pivotal role of the altered regional/whole brain white matter (WM) integrity in stroke-related cognitive impairments. Decreased WM integrity is reportedly associated with cognitive impairments in stroke, suggestive that altered WM integrity may be of pathological in clinical strokes. These findings seem to support the notion that ischemia reduces WM integrity locally or remotely. Thus, it is reasonable to hypothesize that, as a type of stroke, SLI may have a similar mechanism in inducing cognitive disorders.

This study examined the differences in a battery of neuropsychological tests and WM integrity between 27 patients with SLIs in the basal ganglia and 30 healthy controls (HCs). Furthermore, we investigated the relationship between WM disruptions and cognitive dysfunctions.

Methods

Participants

All participants were from the Beijing Aging Brain Rejuvenation Initiative database and (1) scored ≥24 on the Mini-Mental Status Examination; (2) had no history of coronary disease, diabetes mellitus, nephritis, tumors, gastrointestinal disease, or psychiatric illness; and (3) had no history of psychoactive medication use. Their medical history and magnetic resonance imaging scans were separately reviewed by 2 neurologists. We defined lacunar infarcts as round or ovoid lesions of increased signal relative to WM on magnetic resonance imaging T2 and T2-fluid-attenuated inversion recovery images or decreased attenuation similar to cerebrospinal fluid–filled cavi- ties on T1 images, 3 to 15 mm in diameter. All of the patients had lacunar infarcts in the basal ganglia territory (Table I and Figure I).
2 Stroke April 2015

in the online-only Data Supplement). Note that Beijing Aging Brain Rejuvenation Initiative recruited elderly subjects from communities, which could decrease the bias of clinical referral with more severe impairment patients. Considering the confounding effects of WM lesions and small deep infarcts, the present study only included patients with the pure lacunar infarcts.

All participants received a battery of neuropsychological tests such as memory, attention, visuospatial processing, executive function, and language ability (Table II in the online-only Data Supplement).

Image Acquisition and Tract-Based Spatial Statistics

The magnetic resonance imaging data were acquired on a 3.0T Siemens Tim scanner in the Imaging Center for Brain Research, Beijing Normal University. Two sets of diffusion tensor imaging data scans were acquired for every subject and averaged during the data preprocessing. Preprocessing and analyses were performed using PANDA software ( Pipeline for Analyzing Brain Diffusion Images, http://www.nitrc.org/projects/panda/), a diffusion tensor imaging pipeline tool, to generate fractional anisotropy (FA), mean diffusivity (MD) maps for each subject.

Using FMRIB toolbox (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain, http://www.fmrib.ox.ac.uk/fsl), the tract-based spatial statistics on the WM skeleton was performed to compare SLI/HC group differences with the significance threshold set at family-wise error corrected \( P<0.05 \) using the threshold-free cluster enhancement option. Using the digital WM atlas JHUICBM-DTI-81 ( http://cmrm.med.jhmi.edu/), we extracted the mean regional diffusion metrics (ie, FA and MD) from WM fiber where significant tract-based spatial statistics group difference was observed.

Statistical Analysis

For neuropsychological assessment, an ANCOVA was used to test between-group differences (age, sex, and education were included as covariates). We categorized smoking into non, past, and current smokers of <10 and \( \geq 10 \) cigarettes/d. Pearson correlation analyses were performed to explore, only within the SLI group, the relationship between neuropsychological tests and regional FA or MD with significant group difference.

Results

There were no group differences in age, years of education, smoking habits, medical history of hypertension, or hyperlipidemia (Table). Patients had worse cognitive function in general mental status, memory, attention, executive function, and language ability (Table II in the online-only Data Supplement).

Compared with HCs, tract-based statistic results showed that patients had reduced FA across multi-WM fibers, including the body of corpus callosum, forceps minor, bilateral superior corona radiate, left external capsule, bilateral anterior corona radiate, and the genu of corpus callosum. Similar disrupted WM patterns were observed also for MD (Figure 1).

For these regions, we then examined FA/MD relationship with neuropsychological scores only in SLIs. FA in left external capsule was positively correlated with auditory verbal learning test-delay recall (\( r=0.422; \) \( P=0.040 \)), auditory verbal learning test-total (\( r=0.452; \) \( P=0.027 \)), and category verbal

<table>
<thead>
<tr>
<th>Table. Demographics and Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLI (n=27)</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Education, y</td>
</tr>
<tr>
<td>Hypertension (%)</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Non/past/current</td>
</tr>
<tr>
<td>Mini-Mental State Examination</td>
</tr>
</tbody>
</table>

Values are mean±SD or number of participants. HC indicates healthy control; and SLI, silent lacunar infarct.

*The \( P \) values for sex, hypertension, hyperlipidemia, and smoking ratio were obtained using a \( \chi^2 \) test.
fluency test \((r=0.475; \ P=0.019)\) each adjusted for age, sex, and education (Figure 2).

**Discussion**

The present study found the WM alteration in patients with small silent lesion in the basal ganglia. To summarize, SLI patients (1) exhibited cognitive impairments in several domains; (2) showed significantly reduced FA and increased MD across multi-WM regions; and (3) had higher FA value in left external capsule correlated with better cognitive performance.

Our SLI-related cognitive impairment finding is consistent with a previous study, which showed that subcortical brain lacunar infarcts led multiple cognitive function declines.\(^3\) Within SLI, additional post hoc analysis found poorer cognitive performance in visuospatial processing and attention in 16 patients with multi-infarcts than 11 patients with a single SLI and a trend for cognitive decline in multiple SLIs patients, reported also previously.\(^10\)

Compared with HCs, SLI patients displayed significantly reduced FA across several WM regions including the body and genu of body of corpus callosum and genu of corpus callosum, forceps minor, superior corona radiate, anterior corona radiate, and the left external capsule. These regions were either adjacent WM or relatively remote WM to lesions. This may suggest that lesions in basal ganglia not only affect anatomically connected regions but also expand to frontal regions. In pathological essence, with cerebral ischemia, reductions in cerebral blood flow disrupt energy metabolism, accompanied by metabolic stress, and ischemic injury.\(^11\) Cells that undergo severe ischemia may die within minutes of the insult or exhibit a delayed vulnerability. Cytotoxic edema occurrence provokes both a reduction in the extracellular volume fraction and changes in membrane permeability. These events eventually reduce WM integrity locally, at the primary lesion location, because of tissue damage or remotely as a consequence of the loss of afferent synaptic input from distally connected regions or retrograde axonal degeneration.\(^12\) In sum, these above-mentioned studies may provide a reasonable explanation why SLI people have a lower structural integrity. This suggests that all that we found was just only the tip of the iceberg. Combined with increasing evidences from distinct levels such as molecular, cellular, and tissue level, follow-up study of large sample SLI patients will provide more accurate map how SLI account for cognitive impairment.

There are limitations to this study. First, lesion was assessed qualitatively as presence versus absence and not quantified using a quantitative measure (eg, lesion volume). Second, because of the cross-sectional nature of our study, we lacked data such as the cognitive status before the SLI. Finally, we were unable to use an independent sample to confirm our findings and more studies are needed in other populations to examine the finding generalizability. In addition, it would be intriguing to assess the effects of cerebral atrophy in SLI and their combinatorial effects on cognition in the future.

**Acknowledgments**

We appreciate our study participants.

**Sources of Funding**

This work was supported by the Beijing New Medical Discipline Based Group 100270569; Natural Science Foundation of China 81173460 and 81430100 (all to Dr Zhang).

**Disclosures**

In addition to Dr Chen’s full time employment at the Banner Alzheimer’s Institute, he also holds an adjunct professorship at the Beijing Normal University with part-time working pay and partial reimbursement for his visits to Beijing Normal University. The other authors report no conflicts.

**References**


