Brain Atrophy and Cerebral Small Vessel Disease
A Prospective Follow-Up Study

Arani Nitkunan, PhD; Silvia Lanfranconi, MD; Rebecca A. Charlton, PhD; Thomas R. Barrick, PhD; Hugh S. Markus, FRCP

Background and Purpose—Cerebral small vessel disease (SVD) is the most common cause of vascular dementia. Interest in the use of surrogate markers is increasing. The aims of this study were to determine if brain volume was different between patients with SVD and control subjects, whether it correlated with cognition in SVD, and whether changes in brain volume could be detected during prospective follow-up.

Methods—Thirty-five patients (mean age, 68.8 years) who had a lacunar stroke and radiological evidence of confluent leukoaraiosis and 70 age- and gender-matched control subjects were recruited. Whole-brain T1-weighted imaging and neuropsychological testing were performed after 1 year on all patients and after 2 years for the control subjects. Fully automated software was used to determine brain volume and percentage brain volume change. An executive function score was derived.

Results—There was a significant difference in brain volume between the patients with SVD and control subjects (mean ± SD [mL] 1529 ± 84 versus 1573 ± 69, P = 0.019). In the patients with SVD, there was a significant association between brain volume and executive function (r = 0.501, P < 0.05). The mean ± SD yearly brain atrophy rate for patients with SVD and control subjects was significantly different (−0.914% ± 0.8% versus −0.498% ± 0.4%, respectively, P = 0.017). No change in executive function score was detected over this period.

Conclusions—Brain volume is reduced in SVD and a decline is detectable prospectively. The correlation with executive function at a cross-sectional level and the change in brain volume with time are both promising for the use of brain atrophy as a surrogate marker of SVD progression. (Stroke. 2011;42:133-138.)

Key Words: brain atrophy ▪ cerebral small vessel disease ▪ cognitive impairment ▪ longitudinal study ▪ MRI ▪ surrogate marker

Cerebral small vessel disease (SVD) is a major cause of stroke, age-related cognitive decline, and vascular dementia. Despite its importance, few studies have specifically investigated treatment in this stroke subtype.² This is due to a number of issues that complicate assessment of treatment efficacy: the risk of recurrent stroke is relatively low with an annual rate of 0.25%,⁴ the rate of progression to dementia is slow,⁴ and repeated cognitive testing is associated with a learning effect that reduces sensitivity to longitudinal decline. Therefore, large sample sizes are required to determine treatment efficacy when using stroke and dementia as end points. This has led to the suggestion that imaging may provide useful surrogate markers for SVD to assess therapeutic approaches at an early stage.⁵ A number of criteria have been proposed for the definition of an effective surrogate marker for treatment trials.⁶ The first criterion is that the marker must be able to predict the natural course of the disease, that is, it should correlate with relevant clinical features, for example, cognitive function, in both cross-sectional and longitudinal studies.

In multiple sclerosis, imaging parameters have been demonstrated to have high sensitivity for detection of disease activity, which is better than clinical scores.⁷ Brain atrophy has been used as an outcome measure in treatment trials.⁸,⁹ In comparison to multiple sclerosis, there are less data on brain atrophy in SVD with white matter hyperintensity lesion volume being the most widely reported. The progression of lesion volume in SVD has been demonstrated over follow-up periods as short as 2 years.¹⁰ However, correlations between lesion volume and clinical parameters, in particular cognition, have been weak or nonsignificant in a number (but not all) of cross-sectional¹¹–¹³ and longitudinal¹⁴,¹⁵ studies. A further limitation to using lesion load as a surrogate marker is that its measurement is time-consuming and has significant measurement error,¹⁶ although automatic reliable measures are becoming available.¹⁷

An alternative, promising surrogate marker that may be computed from conventional MR sequences is brain volume. Brain volume has been shown to correlate with cognition and
disability scales. However, there are limited data on the rate of atrophy in SVD. An annual rate of 0.5% was found in younger patients with the genetic form of SVD, cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), compared with a rate of 0.38% in normal middle-aged and elderly individuals. A small group of patients with vascular dementia demonstrated a greatly increased rate compared with normal older adults (1.9% annually). Currently, there are no data on the rate of atrophy on patients presenting with lacunar stroke rather than with dementia. It is important to study these individuals because they represent a group in whom treatment, before the onset of dementia, could prevent progression to dementia. In particular, these patients demonstrate significant but subtle cognitive impairments, particularly in executive function.

The aim of this study was to determine whether brain volume is decreased in patients with SVD with respect to normal ageing subjects, whether this decrease was correlated with cognition and disability, and whether changes in brain volume could be detected over a short time period of 1 year.

Methods

Subjects

Patients With SVD

Thirty-five patients presenting with a clinical lacunar stroke syndrome and with a corresponding lacunar infarct on MRI, in combination with confluent radiological leukoaraiosis, were recruited. Patients with other causes of stroke apart from SVD were excluded: cardioembolic source, large cerebral artery stenosis (>50%, large (1.5 cm) subcortical infarcts, or any cortical infarcts. To exclude the effects of acute ischemia on cognition and MRI parameters at baseline, patients were imaged at least 3 months after their last stroke.

Normal Individuals

Seventy stroke-free normal older adults were recruited as part of the GENIE (St George’s Neuropsychology and Imaging in the Elderly) study and were included as the control group. The GENIE subjects were recruited by random sampling from a community population through family doctor lists. Any control subjects with a history of central nervous system disease or major psychiatric disease were excluded. Of the 663 contacted individuals, 408 responded, of whom 158 agreed to participate. Fifty-two were excluded leaving 106 individuals enrolled in the study.

Subject Assessment

Vascular risk factor assessment (blood pressure, diabetes, smoking status, and body mass index) was performed for all subjects as described previously. Modified Rankin score was recorded as a measure of disability.

Follow-Up

All the patients with SVD were invited to return for repeat imaging and neuropsychological assessment 1 year after the baseline appointment and 27 returned for scanning. For these patients, clinical data such as stroke/transient ischemic attack during the interim periods, vascular risk factors, and modified Rankin score were reassessed. As part of the GENIE study, individuals were invited to return for repeat imaging after 2 years and 56 did.

The local research ethics committee approved the study and all the subjects gave informed, written consent.

MRI Acquisition and Analysis

For all participants, longitudinal MRI was performed on a 1.5-T GE Signa MRI system (General Electric, Milwaukee, Wis) with a maximum gradient strength of 22 mT/m. A T1-weighted volume images (spoiled gradient recalled acquisition in steady state; 92 axial slices of 1.5-mm thickness, TR/TE=170/3 seconds, acquisition matrix 256×256×92, field of view 240×240 mm, flip angle 10°) and fluid-attenuated inversion recovery images (TR/TE=9000/120s, inversion recovery time 2200 ms, 28 slices of 5-mm thickness) were acquired. The same imaging sequence was performed at each time point.

Images were transferred to a Sun workstation (Sun Microsystems, Mountain View, Calif) for further analysis. All analyses were performed blinded to the participant’s identity. Brain volume was calculated at baseline using a fully automatic program SIENAX (Structural Image Evaluation, using Normalization, of Atrophy–Cross-sectional; www.fmrib.ox.ac.uk/fsl). This first delineates the brain and skull from T1-weighted images and then normalizes the brain and skull to standard space. Brain volume is reported both as a raw value and relative to normalized skull size to reduce any head size-related variability between subjects.

For each subject, brain volume change was calculated longitudinally from the spoiled gradient recalled acquisition in steady state images using the fully automated image analysis program SIENA (Structural Image Evaluation, using Normalization, of Atrophy; www.fmrib.ox.ac.uk/fsl). SIENAX estimates the exterior surface of the skull and then coregisters the skull image data so that scans obtained at different time points are overlain in the same image space. It computes the brain and nonbrain edges at each time point and calculates the subsequent change in volume presented as a percentage change in brain volume between the scans.

Reproducibility tests on normal volunteers have been performed in previous studies and report an error of 0.15% for brain volume on repeated measures and 0.5% to 1% brain volume accuracy for a single time point (cross-sectional). In the current study, to determine reproducibility within our sample, 2 scans were performed on the same day for 4 SVD subjects and 6 control subjects. SIENAX was then used to determine the immediate reproducibility in this cohort of subjects. The mean±SD percentage brain volume difference between scans was 0.34±0.5% for the patients with SVD and 0.06±0.2% for control subjects.

A semiautomated program using the contour function of the Dispunc software was used to draw automatically around all the lesions on fluid-attenuated inversion recovery images (Christopher Plummer, University College London, London, UK). White matter hyperintensity lesion was defined as white matter areas with increased signal intensity on fluid-attenuated inversion recovery. White matter hyperintensity lesion load was calculated by dividing the white matter hyperintensity lesion volume by the nonnormalized brain volume and then expressed as a percentage. This was performed on 10 random patients with SVD by 2 raters (A.N. and S.L.). The interrater reliability as determined using Pearson correlation coefficient was r=0.996 (P<0.001).

Neuropsychological Assessment

At baseline and follow-up, all subjects completed a range of neuropsychological tests within 1 month of MRI. The tests were chosen to assess a range of cognitive domains, especially executive function. The battery of tests administered is listed in Supplemental Table 1 (available at http://stroke.ahajournals.org). Assessment duration was approximately 30 to 45 minutes.

Statistical Analysis

Cross-Sectional

Differences in demographic characteristics between patients with SVD and control subjects were investigated using Student t tests for continuous data and χ2 tests for discrete data. Group differences in brain volume were assessed using Student t tests. To determine if there were differences in brain volume between groups irrespective of vascular risk factors and lesion load, a multivariate analysis was
performed with these variables as covariates. The following risk factors were used: age, gender, hypertension, smoking, diabetes, and body mass index.

To determine the relationship between baseline brain volume and lesion load, correlation coefficients were obtained (repeated to determine if the relationship was independent of vascular risk factors).

For the SVD cohort, to reduce the number of statistical comparisons, 1 composite neuropsychological scores (general cognition and executive function) were determined using principal components analysis as described previously. The pattern of correlation between brain volume and these 2 scores, a memory score (the logical memory immediate recall score), and current IQ were calculated. These analyses were corrected for age, gender, and premorbid IQ using partial correlations.

**Longitudinal**

The baseline demographic and MR characteristics of the patients who dropped out were compared with patients who attended at the same time points to establish whether the characteristics of the dropouts differed from those who attended.

Annual percentage brain volume change for the control subjects was calculated by dividing the percentage brain volume change between baseline and follow-up after 2 years by 2. The atrophy rate for the 2 groups was then compared using Student t tests (repeated to determine if the relationship was independent of vascular risk factors and lesion load).

The results of the individual neuropsychological tests were compared using paired tests. Where significant changes in cognitive abilities are observed, cognitive change was correlated with atrophy rate.

In the SVD and control cohorts, to identify factors that would predict the possible significant brain atrophy in both groups, multivariate analysis was run with percentage change in brain volume as the dependent variable and the following independent baseline variables: vascular risk factors, lesion load, and normalized brain volume. These factors were also compared in patients with SVD with fast decline (the upper quartile) compared with the remainder of the group to determine if there were any differences.

### Cross-Sectional Study

There were no differences between the groups for age, gender, or smoking status (Table). In patients with SVD, hypertension and diabetes were more common and body mass index higher.

Mean brain volume was smaller in patients with SVD compared with control subjects (mean±SD [mL] 1580±75 versus 1529±84, P=0.003). This difference remained significant after controlling for vascular risk factors (P=0.026), but not after additionally controlling for lesion load (P=0.130).

Mean±SD lesion load (% was greater in patients with SVD compared with control subjects: 3.78±2.52 versus 0.55±0.72 (P=0.0). There was a correlation between brain volume and lesion load (r=-0.352, P=0.0003; Figure 1), which persisted after controlling for vascular risk factors (r=-0.250, P=0.014).

In the SVD cohort, there was a correlation between brain volume and the composite global neuropsychology score (r=0.507, P=0.032) and the composite executive function score (r=0.501, P=0.034). The relationship between brain volume and cognition was independent of lesion load (global neuropsychology r=0.493, P=0.012; executive function r=0.567, P=0.003). There was no correlation with memory (r=0.347, P=0.158), current IQ (r=0.398, P=0.102), or the disability score (r=-0.026, P=0.905).

### Longitudinal Study

There were no significant differences in either the baseline demographic characteristics or brain volume between the patients with SVD that attended at both time points and those who dropped out. No patients or control subjects had a stroke during follow-up.

Mean±SE yearly brain atrophy rate was greater in SVD cases compared with control subjects (0.914±0.16% versus 0.498±0.05%, P=0.017; Figure 2). This is significantly greater than the reported 0.15% brain volume change error. After controlling for vascular risk factors, the significance of this difference reduced to 0.051. It was no longer significant after controlling for baseline lesion load (P=0.280). In contrast, for the patients with SVD, over the period of 1 year, there was no significant change in any of the cognitive scores or the modified Rankin score. In view of the lack of change in cognition or the Rankin score, no correlation between these parameters and change in brain volume could be performed.

The results of the multivariate analysis contained only age as a factor predicting brain atrophy in the SVD cohort and this explained 18% of the variance of yearly brain volume change (P=0.032; Supplemental Table II). A similar multivariate analysis on the control subjects found that gender was the only factor predicting atrophy and explained 10% of the variance (P=0.019). Comparing the upper quartile of patients with increased brain atrophy with the remainder of patients found that the patients with higher age and lower baseline brain volume had a greater atrophy rate (mean±SD age 75.5±6.5 years versus 66.3±8.3 years, P=0.016 and

**Table. Demographic Characteristics of the SVD Subjects Compared With Control Subjects**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
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<th>Follow-Up</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>SVD</td>
<td>P</td>
<td>Control</td>
<td>SVD</td>
<td>P</td>
<td>Control</td>
<td>SVD</td>
</tr>
<tr>
<td>No.</td>
<td>70</td>
<td>35</td>
<td>0.895</td>
<td>67.6</td>
<td>68.8</td>
<td>0.592</td>
<td>56</td>
<td>26</td>
</tr>
<tr>
<td>Age, mean years (SD)</td>
<td>68.5 (9.6)</td>
<td>68.8 (9.3)</td>
<td>0.828</td>
<td>37 (66.1)</td>
<td>18 (69.2)</td>
<td>1.000</td>
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</tr>
<tr>
<td>Male gender, no. (%)</td>
<td>45 (64.3)</td>
<td>24 (68.6)</td>
<td>1×10^-6</td>
<td>29 (51.8)</td>
<td>25 (96.2)</td>
<td>4×10^-5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, no. (%)</td>
<td>37 (52.9)</td>
<td>34 (97.1)</td>
<td>0.002</td>
<td>2 (2.9)</td>
<td>10 (28.6)</td>
<td>25 (45.4)</td>
<td>17 (65.4)</td>
<td>0.163</td>
</tr>
<tr>
<td>Treated diabetes mellitus, no. (%)</td>
<td>2 (2.9)</td>
<td>10 (28.6)</td>
<td>0.002</td>
<td>0</td>
<td>9 (34.6)</td>
<td>1×10^-5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current/exsmoker, no. (%)</td>
<td>36 (52.2)</td>
<td>24 (68.6)</td>
<td>0.278</td>
<td>25 (45.4)</td>
<td>17 (65.4)</td>
<td>0.163</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean(SD) body mass index, kg/m²</td>
<td>25.1 (3.8)</td>
<td>28.0 (5.0)</td>
<td>0.003</td>
<td>25.4 (3.7)</td>
<td>28.2 (4.8)</td>
<td>0.013</td>
<td></td>
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</tr>
</tbody>
</table>
mean±SD baseline brain volume 1458±102 versus 1556±65, \( P=0.007 \), respectively).

**Discussion**

In the analysis of baseline imaging, we demonstrated that brain volume is decreased in patients with SVD compared with age-matched control subjects and confirmed previous studies showing that in SVD brain volume correlates with cognitive scores. In our longitudinal follow-up we demonstrated that the rate of atrophy in patients with SVD, presenting with lacunar stroke and leukoaraiosis, is approximately 1% per annum and twice that found in age-matched control subjects. In contrast, no change in cognition could be detected over this time period. The sensitivity of brain volume measurements to change over time suggests it may be useful as a surrogate marker to monitor disease progress and assess the effect of therapeutic interventions.

The atrophy rate of the control subjects of this study was 0.498%; this is consistent with the results of a community study on 329 aging subjects (annual atrophy rate of 0.38%).20 The mean±SD atrophy rate of the 25 patients with SVD in this study was 0.914%±0.8%, which is almost double the rate reported on 76 patients with CADASIL (0.56%±0.74%)19 and half the rate reported on 9 patients with vascular dementia (1.9%±1.1%).21 The lower rate in CADASIL cohorts is likely to be explained, at least partly, by the younger age of the CADASIL subjects. An additional factor may be the higher rate of hypertension rate in the SVD group (100% versus 24% in the CADASIL group). Hypertension is known to result in brain atrophy.26 The higher rate in patients with vascular dementia may be due to this group being selected for their cognitive impairment and therefore having more severe vascular disease, although the small sample size makes reliable comparisons difficult.

The mechanism of brain atrophy in SVD is not fully understood. The pathological and physiological variables that can affect brain volume have been reviewed in the context of multiple sclerosis.27 Axonal loss, resolution of inflammation and edema, gliosis (through retraction scarring), demyelination, dehydration, normal aging, and anti-inflammatory agents can result in a decrease in brain volume. No direct pathological studies have been performed looking at the histology underlying the changes in brain volume in SVD. It is possible that it is a direct result of microvascular disease. Alternatively, it may occur secondary to other processes such as white matter tract disruption with secondary atrophy. The reduction in the association between SVD and atrophy when white matter hyperintensity lesion load is controlled for would support the second explanation playing a role.

The lack of change in cognitive scores over the time period of 1 year could be explained by a number of factors. First, it is known that the rate of cognitive decline is slow and hence follow-up may be insufficient. Second, it may reflect a lack of sensitivity of the neuropsychology battery or learning effects of repeated assessments. Third, the sample size may be too small to detect a significant change. In view of this lack of
change, a correlation analysis between change in cognitive scores and brain atrophy could not be performed. No significant correlation was found between baseline brain volume or change and modified Rankin score. This may be due to the nonparametric nature of this disability score or that the patients with SVD were minimally disabled with a mean Rankin score of 1.46.

Previous studies correlating brain volume with cognition have measured volume in specific brain compartments, namely the hippocampal and cortical gray matter volume or parenchymal brain volume. Although this allows correlations with specific brain regions, it is more time-consuming and has higher measurement error. Measuring whole brain volume using a fully automated program is fast with low measurement error, which is advantageous when monitoring disease progression or as a surrogate marker. However, evaluation of specific brain region analysis could be interesting and a possibility in future studies.

Brain atrophy fulfills the first criterion for being a surrogate marker; it correlates with relevant clinical features in cross-sectional studies and it changes with time. The next step in establishing brain atrophy as a marker of disease progression is to assess the effect of treatment on the rate of atrophy.

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Disclosures
None.

References


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Supplemental Data
<table>
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<tr>
<th>Neuropsychological test</th>
<th>Test demand</th>
<th>Skill measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini Mental State Examination</td>
<td>Questions testing orientation, registration, attention, recall, language comprehension and apraxia.</td>
<td>General cognitive measure used often in clinical settings</td>
</tr>
<tr>
<td>National Adult Reading Test – Restandardised (NART-R)</td>
<td>Pronunciation of 50 English words that do not follow regular rules – “banal”, “drachm”.</td>
<td>Premorbid intelligence quotient (IQ)</td>
</tr>
<tr>
<td>Vocabulary and Matrix Reasoning subtests of the Wechsler</td>
<td>Vocabulary subtest – need to give a definition of a list of words.</td>
<td>Current IQ</td>
</tr>
<tr>
<td>Abbreviated Scale for Intelligence (WASI)</td>
<td>Matrix subtest – need to choose a picture that logically fit into the pattern of a larger picture.</td>
<td></td>
</tr>
<tr>
<td>Digit Span from the Wechsler Memory Scale III (WMS-III)</td>
<td>Repeat an increasing number of digits forwards and backwards as requested.</td>
<td>Digit Span Backwards - a measure of working memory (a component of executive function). Digit Span Forwards – a measure of attention</td>
</tr>
<tr>
<td>Logical Memory Immediate and Delayed Recall subtests of WMS III</td>
<td>To recall aspects of a story immediately after it is recited and after a 30 minute delay.</td>
<td>Immediate and delayed verbal episodic memory</td>
</tr>
<tr>
<td>Verbal fluency from the Delis-Kaplan Executive Function System (D-KEFS)</td>
<td>To list as many words as possible starting with letter “f”, “a” or “s” in 1 minute.</td>
<td>Generativity/flexibility – an executive function task</td>
</tr>
<tr>
<td>Trails tests from the D-KEFS</td>
<td>5 tests involving identifying all the number “3”s on a sheet of paper, following a dashed line to connect dots, joining serial</td>
<td>Cognitive switching - used as a measure of executive function. Trails motor speed subtest used to control for motor speed.</td>
</tr>
<tr>
<td>Table</td>
<td>The battery of neuropsychology tests that was performed on all the subjects.</td>
<td></td>
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</table>
Table (Online only) Results of multivariate model with backward elimination with the first row showing all independent variables entered into the model and the last row showing that age is the only factor that remains after analysis.
Background and Purpose: Brain small vessel disease (SVD) is the most common cause of vascular dementia. There is increasing interest in finding surrogate markers. The purpose of this study was to determine whether brain volume differed between SVD patients and controls, whether brain volume in SVD patients was related to cognitive function, and whether longitudinal follow-up could detect changes in brain volume.

Methods: Thirty-five patients with atherothrombotic stroke and evidence of confluent cerebral white matter hyperintensities (平均年龄 68.8 岁, SD = 8.0） and 70 age- and sex-matched controls were included. Imaging was performed at baseline and after 1 year. Additionally, SVD patients were re-examined after 2 years. Brain volumes were measured with automated software. Functional scores were obtained.

Results: SVD patients had significantly lower brain volumes (1529±84 mL vs. 1573±69 mL, P = 0.019). SVD patients had a significant correlation between brain volume and cognitive function (r=0.501, P<0.05). The annual rate of brain volume loss was significantly different between SVD patients (–0.914%±0.8%） and controls (–0.498%±0.4%, P=0.017). Functional scores did not change over the follow-up period.

Conclusion: SVD patients had lower brain volumes which further decreased over time. The correlation between brain volume and cognitive function as well as the rate of brain volume loss in SVD patients imply that brain volume could be a promising surrogate measure in the evaluation of treatment effects in SVD.

Keywords: Brain atrophy, Brain small vessel disease, Cognitive dysfunction, Longitudinal study, MRI, Surrogate marker.
Stroke January 2011

人相比 (每年 1.9%)，患有血管性痴呆的一小组患者萎缩率明显增加。与痴呆不同，目前尚缺乏腔隙性卒中患者脑萎缩率的相关数据。然而针对这些患者的研究非常重要，因为在痴呆发生之前对他们进行治疗，可以防止其进展为痴呆。这些患者出现肯定但轻微的认知功能损害，尤其是执行功能。

本研究旨在明确与同年龄正常人相比 SVD 患者脑体积是否减少，这种减少是否与认知和残疾相关，以及脑体积改变是否可在短短的 1 年随访期内被发现。

方法

研究对象

SVD 患者

入组 35 例临床表现腔隙性卒中综合征且 MRI 上显示相应的腔隙性梗死灶以及影像学上显示融合性脑白质疏松的患者。排除 SVD 以外其他原因导致卒中中的患者，包括心源性栓塞、大动脉狭窄>50%、皮层下大梗死灶 (>1.5 cm) 或任何的皮层梗死。患者在最近一次卒中后至少 3 个月行 MRI 检查，以除外急性缺血性基线认知功能和 MRI 参数的影响。

正常人

作为圣乔治老年人神经心理和影像学 (GENIE) 研究的一部分，70 位无卒中的正常老年人被招募为对照组。GENIE 的研究对象来自社区人群的随机抽样，社区人群取自家庭医生的名单。任何有中枢神经系统疾病病史或严重心理疾病的研究对象均被排除。能联系到的 663 位中，有 408 位回复，158 位同意参与研究。其中 52 位被排除，剩下的 106 位入组该研究。

研究对象评估

如前所述，对所有研究对象进行血管危险因素的评估 (血压、糖尿病、吸烟和体重指数) [16]。使用改良的 Rankin 评分来评估残疾程度 [23]。

随访

所有 SVD 患者被邀请在基线评估 1 年后再次进行影像学和神经心理学评估，其中 27 位接受回访。对于这些患者，诸如随访期间卒中 / 短暂性脑缺血发作相关的临床数据、血管危险因素和改良 Rankin 评分被重新评估。作为 GENIE 研究的一部分，(对照组) 的研究对象被邀请 2 年后回来再次进行影像学评估，其中 56 位接受回访。

该研究得到当地研究伦理委员会的批准，所有研究对象均提交书面知情同意书。

MRI 采集与分析

使用最大梯度强度为 22 mTm⁻¹ 的 1.5 T GE Signa MRI 系统 (通用电气，密尔沃基，威斯康星) 对所有研究对象进行纵向 MRI 扫描。获取 T1 加权像 (毁损稳态梯度回返采集)；22 个厚度为 1.5 mm 的轴位层面，TR/TE=17/3 s, 采集矩阵 256×256×92，视场 240×240 mm，回转角 10°) 和液体衰减反转恢复脉冲序列成像 (TR/TE=9000/120 s，反转恢复时间 2200 ms，28 个厚度为 5 mm 的层面)。各时间点均重复同样的成像序列。

图像被传送至太阳工作站 (Sun workstation)(Sun Microsystem, Mountain View, 加里福利亚) 进一步分析。分析时对研究对象身份采用盲法。使用全自动程序 SIENAX (Structural Image Evaluation, using Normalization, of Atrophy Cross-sectional; www.fmrib.ox.ac.uk/fsl) 计算基线期脑体积 [24]。该程序首先从 T1 加权像界定脑和颅骨，然后将脑和颅骨标准化，使之成为标准体积，报告的结果同时给出脑体积原始值和与标准化颅骨大小相比得到的相对值，以减小不同研究对象的不同头部大小所导致的变异。

使用全自动图像分析程序 SIENA (Structural Image Evaluation, using Normalization, of Atrophy; www.fmrib.ox.ac.uk/fsl) 从毁损稳态梯度回返采集图像中对所有研究对象进行纵向计算 [25]。SIENA 先估算颅骨外表面，然后对颅骨图像进行配准，使不同时间点获得的扫描结果平铺成相同的图像大小。它计算每个时间点脑和非脑的界限，并计算每次扫描的脑体积改变百分比。

既往研究已经对正常自愿者进行了重复检测，重复测量脑体积的误差为 0.15%，单一时间点 (横断面) 测量的准确性误差为 0.5%-1% [24]。本研究中，为了确认样本的可重复性，4 位 SVD 患者和 6 位对照者在同一天进行了两次扫描。然后使用 SIENAX 来确认该队列研究对象的可重复性。SVD 患者两次扫描脑体积的差别百分比为 0.34%±0.5%( 平均值±SD)，对照组则为 0.06%±0.2%。

带有 Dispunc 软件中测量轮廓函数的半自动软件被用于自动地在液体衰减反转恢复脉冲序列图像 (Christopher Plummer, 伦敦大学学院，伦敦，英国) 上画出血病灶轮廓。
反转恢复脉冲序列图像上信号强度增加的白质区。白质高信号病灶负荷是通过白质高信号病灶体积除以标准化脑体积来计算，并用百分比表示。两位评价者（A.N.和S.L.）在随机的10位SVD患者上进行计算。两位评价者之间的可靠性用Pearson相关系数来确定，*r* =0.996（*P*=0）。

### 神经心理学评估

在基线和随访过程中，所有研究对象在MRI检查后一个月内完成一系列神经心理学测试，用以评估认知功能，特别是执行功能。这一系列测试列于附表I(可见于http://stroke.ahajournals.org)。评估持续时间接近30-45分钟。

### 统计分析

#### 横断面分析

SVD患者和对照组在人口统计学方面的差异通过Student *t*检验和χ²检验来评估，前者评估连续型数据，后者评估离散型数据。脑体积的组间差异通过Student *t*检验来评估。为排除血管危险因素和病灶负荷对结果的影响，以这些变量为协变量进行多因素分析来确定脑体积的组间差异。这些危险因素包括：年龄、性别、高血压、吸烟、糖尿病和体重指数。

### 纵向分析

对退出患者和完成研究的患者的基线人口统计学和MR特征进行了比较，以明确这些特征在两者间是否存在差异。

以基线和随访2年的脑体积百分比之差除以2来计算对照组脑体积年变化百分比。使用Student *t*检验比较两组的萎缩率（重复检验以明确这一关系是否与血管危险因素和病灶负荷无关）。

### 结果

#### 横断面研究

两组在年龄、性别和吸烟状态方面无差异(表)。SVD患者中高血压和糖尿病更多见，体重指数更高。

与对照组相比，SVD患者平均脑体积更小（平均值±SD[mL]: 1580±75 对1529±84, *P*=0.003）。校正了血管危险因素后，这一差异仍然显著(*P*=0.026); 但进一步校正了病灶负荷后，差异不再显著(*P*=0.130)。

与对照组相比，SVD患者病灶负荷（平均值±SD[%]): 3.78±2.52 对0.55±0.72(*P*=0.0002)。脑体积与病灶负荷存在相关性（*r*=-0.352, *P*=0.0003; 图1），校正血管危险因素后，该相关性仍然存在（*r*=-0.250, *P*=0.014）。

在SVD患者中，脑体积与综合的神经心理评分（*r*=-0.507, *P*=0.032）和综合的执行功能（*r*=-0.501, *P*=0.034）存在相关性。脑体积与认知功能的关系独立于病灶负荷（全神经心理评分：*r*=-0.493, *P*=0.012; 执行功能：*r*=-0.567, *P*=0.003)。（脑体积）与记忆力（*r*=-0.347, *P*=0.158)、目前智商（*r*=-0.398,

### 表

<table>
<thead>
<tr>
<th></th>
<th>对照组</th>
<th>SVD</th>
<th><em>P</em></th>
<th>对照组</th>
<th>SVD</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>人数</td>
<td>70</td>
<td>35</td>
<td></td>
<td>56</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>年龄，平均岁数 (SD)</td>
<td>68.5 (9.6)</td>
<td>68.8 (9.3)</td>
<td>0.895</td>
<td>67.6 (9.3)</td>
<td>68.8 (8.8)</td>
<td>0.592</td>
</tr>
<tr>
<td>男性，人数 (%)</td>
<td>45 (64.3)</td>
<td>24 (68.6)</td>
<td>0.828</td>
<td>37 (66.1)</td>
<td>18 (69.2)</td>
<td>1.000</td>
</tr>
<tr>
<td>高血压，人数 (%)</td>
<td>37 (52.9)</td>
<td>34 (97.1)</td>
<td>1×10⁻⁴</td>
<td>29 (51.8)</td>
<td>25 (96.2)</td>
<td>4×10⁻³</td>
</tr>
<tr>
<td>糖尿病，人数 (%)</td>
<td>2 (2.9)</td>
<td>10 (28.6)</td>
<td>0.0002</td>
<td>0</td>
<td>9 (34.6)</td>
<td>1×10⁻³</td>
</tr>
<tr>
<td>高血压、糖尿病，人数 (%)</td>
<td>36 (52.2)</td>
<td>24 (68.6)</td>
<td>0.278</td>
<td>25 (45.4)</td>
<td>17 (65.4)</td>
<td>0.163</td>
</tr>
<tr>
<td>平均 (SD)体重指数，kg/m²</td>
<td>25.1 (3.8)</td>
<td>28.0 (5.0)</td>
<td>0.003</td>
<td>25.4 (3.7)</td>
<td>28.2 (4.8)</td>
<td>0.013</td>
</tr>
</tbody>
</table>
$P=0.102$) 及残疾评分 ($r=-0.026$, $P=0.905$) 无相关性。

纵向研究

退出的 SVD 患者与完成研究的患者在基线人口统计学特征和脑体积方面无显著差异。随访过程中患者和对照组均未发生卒中。

与对照组相比，SVD 患者的年脑萎缩率 (平均值 ±SE) 更高 (0.914%±0.16% 对 0.498%±0.05%, $P=0.017$；图 2)。这一结果显著高于报道的脑体积改变误差0.15%[24]。校正血管危险因素后，这一差异的显著性降为 $0.051$。校正基线病灶负荷后，这一差异不再显著 ($P=0.280$)。相比之下，SVD 患者 1 年后认知功能评分或改良 Rankin 评分没有显著变化。鉴于认知功能或 Rankin 评分无变化，因此可以认为脑体积的改变与这些参数无关。

多因素分析结果显示，仅年龄是 SVD 患者中脑萎缩的预测因素，解释了每年脑体积改变差异的 $18\%$ ($P=0.032$，附表 II)。对照组类似的多因素分析发现，性别是其脑萎缩的唯一预测因素，该因素解释了差异的 $10\%$ ($P=0.019$)。通过比较脑萎缩更重的前四分之一患者和其余患者，发现年龄越大和基线脑体积越小的患者脑萎缩率越高 (分别为：年龄 [ 平均值 ±SD], 75.5±6.5 岁 对 66.3±8.3 岁, $P=0.016$ 以及基线脑体积 [ 平均值 ±SD], 1458±102 对 1556±65, $P=0.007$)。

讨论

通过基线影像分析，我们发现与按年龄匹配的对照组相比，SVD 患者脑体积减少，并验证了既往的研究结果：SVD 患者脑体积与认知功能评分相关。在纵向随访中，我们证实了表现为腔隙性卒中和脑白质疏松的 SVD 患者脑萎缩率为每年 1%，是按年龄匹配的对照组的 2 倍。相比之下，随访期间未发现认知功能改变。脑体积随时间改变的测量敏感性说明这可以作为监测疾病进展和评估治疗干预效果的替代指标。

本研究对照组脑萎缩率为 0.498%，这一结果与纳入 329 位老年人的社区研究 ( 脑萎缩率为 0.38%) 一致 [20]。本研究 25 位 SVD 患者脑萎缩率 ( 平均值 ±SD) 为 0.914%±0.8%，这几乎是报道的 76 位 CA-
DASIL 患者脑萎缩率 (0.56%±0.74%) 的 2 倍，是报道的 9 位血管性痴呆患者脑萎缩率 (1.9%±1.1%) 的一半。CADASIL 患者脑萎缩率更低，部分因为 CADASIL 患者年龄较小。另一个原因可能是 SVD 组高血压比例更高 (100% 对 CADASIL 组的 24%)。已知高血压可导致脑萎缩 [26]。虽然样本量小难以进行可靠的比较，血管性痴呆患者脑萎缩率更高可能是由于该组研究对象入组时均存在认知功能障碍，因此血管病变更严重。

SVD 患者脑萎缩机制尚不清楚。在多发性硬化患者中，已报道病理和生理因素可影响脑体积 [27]。轴突消失、炎症和水肿退化、神经胶质增生 (通过收缩瘢痕)、脱髓鞘、脱水、正常老化以及抗炎物质等均可导致脑体积减少。尚无直接病理学研究阐明 SVD 患者脑体积改变的组织学基础。它可能是微血管病变的直接结果。另外，脑萎缩也可能继发于其他过程，例如白质传导束破坏导致继发脑萎缩。校正了白质高信号病灶负荷后，SVD 和萎缩的相关性降低，说明后一种解释发挥了一定作用。

在 1 年的随访期内认知功能评分无改变可解释为以下原因：首先，认知功能通常下降缓慢，因此随访时间可能不够。其次，它可能反映了神经心理学测试敏感性较低或重复评估时学习效应影响了测评结果。第三，样本量可能太小，不足以发现显著变化。鉴于未发现认知功能改变，因此不能进行认知功能评分改变和脑萎缩的相关性分析。基线脑体积或脑体积变化与改良 Rankin 评分未见显著相关。这可能是由于该残疾评分的非参数性质或是因为 SVD 患者功能残疾很轻，平均 Rankin 评分只有 1.46 分。

既往的认知功能和脑体积相关性研究测定了特定脑区，即海马和皮层灰质体积 [12,18] 或脑实质体积 [13]。虽然这使得（脑萎缩）与特定脑区相关，但该法更耗时，且测量误差更高。全自动程序测量全脑体积快速且测量误差小，这些特点使其在监测疾病进展或用作替代指标时更具优势。然而，评估特定脑区域非常有趣，将来也可能做这样的研究。

脑萎缩完全符合替代指标的第一条标准：在横断面研究中它与有关临床特征相关，同时也随时间而改变。确定脑萎缩作为疾病进展指标的下一步是用脑萎缩率来评估疗效。


