New Silent Cerebral Infarction in Patients with Acute Non-Cerebral Amyloid Angiopathy Intracerebral Hemorrhage as a Predictor of Recurrent Cerebrovascular Events

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Background: The aim of this study was to investigate the incidence and related risk factors of new silent cerebral infarction in patients with acute non-cerebral amyloid angiopathy (non-CAA) intracerebral hemorrhage (ICH) and to explore clinical cerebrovascular event recurrence within 1 year.

Material/Methods: This prospective study observed 152 patients with non-CAA ICH diagnosed by computed tomography within 3 days after onset. All patients underwent magnetic resonance imaging on day 14 to identify silent cerebral infarction, and their subsequent clinical cerebrovascular events were followed up regularly within 1 year.

Results: Of the 152 patients, 46 (30.26%) had silent cerebral infarctions. Multiple logistic regression analysis revealed that the white blood cell (WBC) count, cerebral microbleeds (CMBs), and leukoaraiosis were silent cerebral infarction risk factors. At 1-year follow-up, 34 (22.37%) had clinical cerebrovascular events, with 8 (23.53%) having vascular-related deaths. Multiple logistic regression analysis showed that silent cerebral infarction was the only independent predictor of future clinical cerebrovascular events.

Conclusions: Silent cerebral infarction is common during acute non-CAA ICH and is independently related to WBC counts, CMBs, and leukoaraiosis. The risk of clinical cerebrovascular events in non-CAA ICH patients with silent cerebral infarction increases in the following year; thus, silent cerebral infarction may be a useful predictor of recurrent cerebrovascular events.

MeSH Keywords: Cerebral Amyloid Angiopathy • Cerebral Small Vessel Diseases • Leukoaraiosis

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Background

Intracerebral hemorrhage (ICH) caused higher mortality and disability rates among all types of stroke [1]. Spontaneous ICH accounts for 10–30% of all stroke cases, which seriously affects the quality of life of patients and imposes heavy economic burden on society and family [2]. Cerebral infarction and ICH are 2 independent diseases. Although some diseases, such as cerebral amyloid angiopathy (CAA) and moyamoya disease, can cause both cerebral infarction and ICH [3], stroke patients usually only have one of them. With the development in magnetic resonance imaging (MRI) technology, especially the application of diffusion-weighted imaging (DWI), there have been continuous studies on the coexistence of cerebral infarction and ICH in stroke patients, and the detection rate is continuously increasing. Previous studies have found that silent cerebral infarction is common in patients with cerebral infarction, CAA, subarachnoid hemorrhage, and ICH [4–7]. There are many studies on DWI lesions in ICH, but there are currently only a few studies on the relationship between silent cerebral infarction and the long-term prognosis of patients. The aim of this study was to assess the risk factors of silent cerebral infarction in patients with non-CAA ICH and to explore the correlation between silent cerebral infarction and recurrent clinical cerebrovascular events within 1 year.

Material and Methods

From January 2016 to June 2017, 152 patients with acute non-CAA ICH were enrolled in the Department of Neurology, Shuyang People’s Hospital, Jiangsu Province, and were regularly followed up within 1 year after onset of disease. The study was carried out in accordance with the recommendations of the 2014 Guidelines for Cerebral Hemorrhage and Cerebral Infarction in China and the Academic Committee and Ethics Committee of Shuyang People’s Hospital, as well as the Declaration of Helsinki. The protocol was approved by the Academic Committee and Ethics Committee of Shuyang People’s Hospital. All subjects gave written informed consent prior to their inclusion in the study.

Inclusion criteria

Patients with acute ICH for the first time whose diagnosis and neurological deficit scores were according to the criteria and scoring standards established by the Fourth National Conference on Cerebrovascular Diseases in 1996 and confirmed by computed tomography (CT) or MRI were included.

Exclusion criteria

We excluded patients with clearly identified cerebral infarction or embolism; hemorrhagic cerebral infarction; recent active bleeding, bleeding disorders, or bleeding tendency; severe heart, liver, or kidney dysfunction; platelet count <100×10^9/L and fibrinogen ≤1.0 g/L; recent surgical and traumatic injuries; obvious surgical indications (cerebral lobe or shell nucleus hemorrhage >30 mL, cerebellar hemisphere hemorrhage >15 mL, and drainage for ventricular casting); definite vascular lesions (such as aneurysm, arteriovenous malformation, and cavernous hemangioma); or those with family members requiring craniotomy [8]. Probable and possible ICHs caused by CAA were excluded based on the modified Boston standard.

Data collection

General clinical data, laboratory data, and imaging data of the patients were collected. The severity of neurological impairment at the time of admission was evaluated by the stroke scale of the US National Institutes of Health and the Glasgow Coma Scale. All patients were diagnosed with ICH by head CT examination within 3 days, and head MRI (Germany Siemens 3.0T MR) examination was performed on the 14th day after ICH. For MRI examination, sequences included T1-, T2-, DWI, and susceptibility-weighted imaging (SWI). All scans were performed by skilled radiologists, and image information, including silent cerebral infarction (high signal on DWI sequence), cerebral microbleeds (CMBs), and leukoaraiosis, were randomly read and recorded by 2 radiologists blinded to clinical information [9].

Silent cerebral infarction, CMBs, leukoaraiosis, and end events definition

Silent cerebral infarction was defined as a high-signal intensity lesion on DWI with accompanying low-signal intensity on ADC. The high-signal intensity lesions in the area of the hemisoma and surrounding tissue were excluded [8]. Asymptomatic was defined as the absence of new symptoms such as abnormal sensation, limb weakness, or deterioration of the original nervous system function [10]. CMBs were defined as a circular and quasi-circular signal reduction shadow with a diameter of 2–5 mm on SWI, with clear boundary and no surrounding edema, and calcification, peripheral space, and small-vein vessels excluded [11,12]. Cerebral leukoaraiosis was defined as long spots, plaques, or fused long-T2 signal image of white matter around the ventricle or the central part of the hemispheric circle [13,14].

Clinical cerebrovascular end events were defined as cerebral infarction, ICH, and subarachnoid hemorrhage. Cerebrovascular-related deaths include deaths from recurrent cerebral infarction ICH and subarachnoid hemorrhage, excluding suicide and cancer-, infection-, and cardiovascular-related deaths.
Follow-up

Patients were followed up by telephone interview. Those who were unable to answer the orientation questions underwent an agent interview. Every 3 months after the stroke, patients were asked to answer standardized follow-up questions. Cases of recurrent stroke were cross-checked with the treating hospitals to ensure the accuracy of diagnosis. In case of suspected stroke recurrence without hospitalization, the case was adjudicated by the trial executive committee. Data collected included stroke recurrence and death caused by recurrent cerebrovascular events. Mortality was defined as death from cerebrovascular events confirmed by either a death certificate from the local citizen registry or records from the treating hospital.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and were analyzed with the independent-sample t test. Categorical data, shown as count and percentage, were analyzed with either the chi-square test or the Fisher’s exact test. Ranked ordinal data were analyzed with the Wilcoxon rank sum test. Multivariate logistic regression analysis was used for independent variables with significant significance through

![Figure 1](image-url). The diffusion-weighted imaging of magnetic resonance imaging (A is cerebral bleeds; B is silent cerebral infarction).
single-factor analysis. Two-tailed P values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 17.0 (IBM, Armonk, NY).

Results

Risk factors analysis of silent cerebral infarction

Of 152 patients with non-amyloid ICH, 46 (30.26%) were found to have silent cerebral infarction (Figure 1). Compared with patients without silent cerebral infarction, patients with silent cerebral infarction had lower levels of urea nitrogen (P=0.024), higher white blood cell (WBC) counts (P=0.005), more CMBs (P<0.001), more severe leukoaraiosis (P<0.001), and more lacunar infarctions (P=0.003) (Table 1).

Multivariate logistic regression analysis showed that CMBs, WBC counts, and leukoaraiosis were independent risk factors for silent cerebral infarction (Table 2).

Risk factors for recurrence of cerebrovascular events

During the 12-month follow-up, 34 (22.37%) patients had recurrent cerebrovascular events. Among them, 8 died of related cerebrovascular events. During the 12-month follow-up, the recurrence of cerebrovascular events was associated with diabetes, atrial fibrillation, smoking, or alcohol consumption, but was significantly associated with urea nitrogen (P=0.001), CRP (P=0.028), silent cerebral infarction (P<0.001), and leukoaraiosis (P=0.044). Compared with patients without cerebrovascular events, those with cerebrovascular events had higher CRP, lower urea nitrogen, higher incidence of silent cerebral infarction, and more severe leukoaraiosis (Table 3).

Multivariate logistic regression analysis showed that silent cerebral infarction was an independent predictor of clinical cerebrovascular events within 1 year after the onset of ICH. Older patients tended to have higher incidence of cerebrovascular events (Table 4).

Discussion

Silent cerebral infarction can be found not only in patients with cerebral infarction, but also in patients with ICH or subarachnoid hemorrhage [4,6,15]. Prior studies have found that silent cerebral infarction was observed in 13–41% of patients with acute ICH [16,17]. The present study found silent cerebral infarction in 30.26% of patients with non-CAA ICH. As in previous studies, we also found that the presence of 2 MRI markers for small-vessel diseases (SVDs) – including leukoaraiosis and CMBs – are associated with new DWI lesions in non-CAA ICH patients [5,18]. Two types of SVD (arteriopathy and CAA) have been proposed to be associated with deep and lobar ICH, respectively [8].

The pathophysiological mechanism of silent cerebral infarction is related to atherosclerosis and microembolism of arterioles less than 100 μm in diameter, which is a special type of lacunar infarction. In fact, a new DWI lesion has also been recognized as a neuroimaging marker for SVD [19]. Because of the relatively mild degree of ischemia, the short duration of ischemia, or the rapid establishment of good collateral circulation, there is no evidence of transient ischemic attack or cerebral infarction in patients with silent cerebral infarction, leaving only evidence of neuroimaging changes. Cerebral blood flow and brain metabolism in patients with silent cerebral infarction were studied by positron-emission tomography. Cerebral cortex blood flow was decreased slightly and oxygen consumption increased significantly in patients with silent cerebral infarction, suggesting insufficient blood perfusion in local brain tissue. However, examination of cerebral infarction patients with symptoms and signs of neurological impairment showed a consistent decrease in blood flow and oxygen metabolism in the brain [20].

The changes in cerebral blood flow, brain metabolism, and blood-brain barrier and the release of inflammatory factors caused by ICH may be the pathological mechanism of silent cerebral infarction in non-CAA ICH [3,21].

These changes not only cause dysfunction of blood flow regulation and luminal occlusion, but also cause the vessel wall to become disrupted and fragmented, making it prone to blood extravasation and microaneurysm formation [22,23]. Another possible explanation is that the presence of silent cerebral infarction is a more severe vasculopathy that can lead to more CMBs or leukoaraiosis.

To the best of our knowledge, this is the first report on the association of WBC counts with silent cerebral infarction after non-CAA ICH. The CAPRIE trial [24], which included 18 588 patients with ischemic stroke, myocardial infarction, or peripheral vascular disease, found that increased WBC counts, especially neutrophil count, were independent risk factors for recurrent ischemic events in high-risk groups. The study also found that WBC counts started significantly higher than baseline at 1 week before ischemic events, but not earlier. In a prospective cohort study based on multiethnic urban populations, Elkind et al. (2005) found in stroke risk increased by 20% for each additional cell count of 1.8×10⁷ cells/L on a baseline basis for 3103 people without stroke with average age of 52 years. Adjusted for other stroke risk factors, other ischemic events also increased. They suggested that elevated levels of WBC relative to baseline were independent risk factors for stroke.
Table 1. Single risk factors analysis of silent cerebral infarction.

| Characteristic                        | Control (n=106) | Observation (n=46) | t/Z/-value | P-value |
|---------------------------------------|----------------|-------------------|------------|---------|
| Age (years)                           | 59.70±11.30    | 60.46±9.01        | 0.708      | 0.480   |
| Sex                                   |                |                   |            |         |
| Male                                  | 73 (68.87)     | 34 (73.91)        | 0.392      | 0.531   |
| Female                                | 33 (31.13)     | 12 (26.07)        |            |         |
| Coronary heart disease                | 16 (15.09)     | 14 (30.43)        | 0.432      | 0.511   |
| Hypertension                          | 93 (87.73)     | 38 (82.61)        | 1.758      | 0.415   |
| Diabetes                              | 10 (9.43)      | 8 (17.39)         | 1.946      | 0.163   |
| Smoking                               | 50 (47.17)     | 23 (50.00)        | 0.103      | 0.748   |
| Drinking                              | 48 (45.28)     | 27 (58.69)        | 2.309      | 0.129   |
| Lacunar infarction                    | 25 (23.58)     | 22 (47.83)        | 8.825      | 0.003   |
| Atrial fibrillation                   | 4 (3.77)       | 2 (4.35)          | 0.028      | 0.867   |
| Coronary heart disease                | 4 (3.77)       | 4 (8.69)          | 1.559      | 0.212   |
| Stroke history                        | 29 (27.36)     | 7 (15.22)         | 2.616      | 0.106   |
| Glucose (mmol/L)                      | 7.09±2.08      | 6.97±2.22         | 2.453      | 0.022   |
| Hematoma volume (ml)                  | 12.21±10.80    | 11.16±11.14       | 0.538      | 0.592   |
| Total protein (g/L)                   | 63.42±8.36     | 65.32±7.54        | 1.323      | 0.188   |
| Albumin (g/L)                         | 38.21±6.11     | 39.69±5.54        | 1.403      | 0.163   |
| Systolic blood pressure (mmHg)        | 164.45±24.33   | 170.00±23.77      | 1.300      | 0.196   |
| Diastolic blood pressure (mmHg)       | 97.82±18.06    | 99.43±12.85       | 0.625      | 0.533   |
| NIHSS score at admission              | 8.85±6.84      | 8.59±6.95         | 0.216      | 0.839   |
| GCS                                   | 13.65±2.70     | 14.04±2.76        | 0.878      | 0.381   |
| Total bilirubin (mmol/L)              | 12.23±5.34     | 11.11±6.62        | 1.109      | 0.269   |
| Direct bilirubin (mmol/L)             | 2.24±1.18      | 2.30±1.46         | 0.242      | 0.809   |
| Cholesterol (mmol/L)                  | 4.65±0.92      | 4.51±0.91         | 0.874      | 0.384   |
| Triglyceride (mmol/L)                 | 1.67±1.25      | 1.49±0.92         | 0.865      | 0.389   |
| High-density lipoprotein Cholesterol (mmol/L) | 1.17±0.29  | 1.19±0.29         | 0.525      | 0.601   |
| Low-density lipoprotein Cholesterol (mmol/L) | 2.29±0.63  | 2.39±0.62         | 0.866      | 0.389   |
| Blood urea nitrogen (mmol/L)          | 5.41±1.66      | 4.74±1.67         | 2.281      | 0.024   |
| Creatinine (mmol/L)                   | 67.71±42.17    | 63.21±12.35       | 0.403      | 0.965   |
| White blood cells (10^9/L)            | 7.43±1.86      | 8.40±2.01         | 2.874      | 0.005   |
| Red blood cells (10^12/L)             | 4.73±0.55      | 4.66±0.49         | 0.734      | 0.464   |
| Platelets (10^9/L)                    | 208.41±68.69   | 208.50±52.86      | 0.008      | 0.994   |
| Fibrinogen (g/L)                      | 3.18±0.92      | 3.36±0.89         | 1.129      | 0.261   |
| C reactive protein (mg/L)             | 5.86±5.05      | 5.24±3.59         | 0.781      | 0.437   |
| Pneumonia                             | 16 (15.09)     | 12 (26.08)        | 0.837      | 0.360   |
| CMBs                                  | 38 (35.85)     | 32 (69.57)        | 14.678     | 0.000   |
Table 1 continued. Single risk factors analysis of silent cerebral infarction.

| Characteristic       | Control (n=106) | Observation (n=46) | t/Z/\(^2\)-value | P-value |
|----------------------|-----------------|--------------------|-------------------|---------|
| Leukoaraiosis        |                 |                    |                   |         |
| No                   | 47 (44.34)      | 7 (15.22)          |                   |         |
| Mild                 | 41 (38.68)      | 15 (32.61)         | 4.712             | 0.000   |
| Moderate             | 15 (14.15)      | 16 (34.78)         |                   |         |
| Severe               | 3 (2.83)        | 8 (17.39)          |                   |         |
| Prognosis            |                 |                    |                   |         |
| Cerebrovascular event| 13 (12.26)      | 21 (45.65)         | 20.593            | 0.000   |
| Death                | 3 (4.72)        | 5 (10.87)          | 4.158             | 0.041   |

Values are presented as mean ± deviation or n (%). NIHSS – National Institute of Health Stroke Scale; GCS – Glasgow Coma Score; CMBs – cerebral microbleeds.

Table 2. Multivariate logistic regression analysis of significant risk factors for silent cerebral infarction.

| Factor                  | OR   | 95% CI          | P value |
|-------------------------|------|-----------------|---------|
| CMBs                    | 3.799| 1.294–11.153    | 0.015   |
| Urea                    | 0.832| 0.629–1.000     | 0.197   |
| White blood cell        | 1.433| 1.122–1.829     | 0.004   |
| Lacunar infarction      | 1.917| 0.699–5.253     | 0.206   |
| Leukoaraiosis           | 1.897| 1.032–3.488     | 0.039   |

OR – odds ratio; CI – confidence interval; CMBs – cerebral microbleeds.

Table 3. Single risk factor analysis for recurrence of cerebrovascular events.

| Characteristic          | Recurrence (n=34) | Non-recurrence (n=118) | t/Z/\(^2\)-value | P-value |
|-------------------------|-------------------|------------------------|-------------------|---------|
| Age (years)             | 64.21±11.28       | 59.77±10.66            | 2.109             | 0.037   |
| Sex                     |                   |                        |                   |         |
| Male                    | 26 (68.42)        | 81 (68.64)             | 0.776             | 0.378   |
| Female                  | 8 (23.53)         | 37 (31.36)             |                   |         |
| Coronary heart disease  | 2 (5.88)          | 6 (5.08)               | 0.034             | 0.856   |
| Hypertension            | 29 (85.29)        | 102 (86.44)            | 1.424             | 0.491   |
| Diabetes                | 4 (11.76)         | 14 (11.86)             | 0.000             | 0.987   |
| Smoking                 | 16 (47.06)        | 57 (49.89)             | 0.016             | 0.898   |
| Drinking                | 16 (47.06)        | 59 (50.00)             | 0.091             | 0.762   |
| Lacunar infarction      | 11 (32.35)        | 36 (30.51)             | 0.042             | 0.838   |
| Atrial fibrillation     | 1 (2.94)          | 5 (4.24)               | 0.117             | 0.732   |
| Coronary heart disease  | 2 (5.88)          | 6 (5.08)               | 0.034             | 0.854   |
| Stroke history          | 7 (20.59)         | 29 (24.58)             | 0.232             | 0.630   |
Table 3 continued. Single risk factor analysis for recurrence of cerebrovascular events.

| Characteristic                               | Recurrence (n=34) | Non-recurrence (n=118) | t/Z²-value | P-value |
|----------------------------------------------|-------------------|------------------------|------------|---------|
| Glucose (mmol/L)                             | 6.72±2.26         | 7.16±2.08              | 2.453      | 0.022   |
| Hematoma volume (ml)                         | 10.31±10.86       | 12.35±10.38            | 0.338      | 0.962   |
| Total protein (g/L)                          | 63.23±8.10        | 64.20±8.17             | 0.587      | 0.558   |
| Albumin (g/L)                                | 39.42±4.96        | 38.44±6.22             | 0.840      | 0.402   |
| Systolic blood pressure (mmHg)               | 171.50±22.07      | 164.58±24.68           | 1.472      | 0.413   |
| NIHSS score at admission                     | 7.53±6.32         | 9.13±6.99              | 1.199      | 0.232   |
| GCS                                          | 14.50±1.33        | 13.56±2.75             | 1.927      | 0.056   |
| Total bilirubin (mmol/L)                     | 10.62±6.27        | 12.26±5.58             | 1.466      | 0.145   |
| Direct bilirubin (mmol/L)                    | 2.37±1.51         | 2.22±1.20              | 0.591      | 0.555   |
| Triglyceride (mmol/L)                        | 1.52±1.00         | 1.65±1.21              | 0.545      | 0.586   |
| High-density lipoprotein Cholesterol (mmol/L)| 1.20±0.30         | 1.17±0.29              | 0.530      | 0.597   |
| Low-density lipoprotein Cholesterol (mmol/L) | 2.30±0.65         | 2.33±0.62              | 0.185      | 0.853   |
| Urea (mmol/L)                                | 4.54±1.11         | 5.42±1.77              | 3.484      | 0.001   |
| Creatinine (mmol/L)                          | 60.72±14.77       | 68.00±39.52            | 1.052      | 0.295   |
| Uric acid (mmol/L)                           | 262.47±74.86      | 274.03±81.54           | 0.723      | 0.471   |
| White blood cells (10⁹/L)                    | 7.60±2.05         | 7.75±1.94              | 0.388      | 0.698   |
| Red blood cells (10¹²/L)                     | 4.59±0.58         | 4.75±0.51              | 1.525      | 0.129   |
| Platelets (10⁹/L)                            | 205.82±56.70      | 209.20±65.98           | 0.270      | 0.787   |
| Fibrinogen (g/L)                             | 3.09±0.77         | 3.28±0.95              | 1.046      | 0.297   |
| C-reactive protein (mg/L)                    | 4.27±2.49         | 6.05±4.85              | 2.884      | 0.005   |
| Pneumonia                                    | 4 (11.76)         | 24 (20.34)             | 1.291      | 0.256   |
| CMBs                                         | 18 (52.94)        | 52 (44.07)             | 0.837      | 0.360   |
| Silent cerebral infarction                   | 21 (61.76)        | 13 (11.07)             | 20.593     | 0.000   |
| Leukoaraiosis                                | 2.21±2.3          |                        |            |         |
| No                                           | 5 (14.71)         | 41 (34.75)             |            |         |
| Mild                                         | 11 (32.35)        | 44 (37.29)             |            |         |
| Moderate                                     | 11 (32.35)        | 18 (47.06)             |            |         |
| Severe                                       | 2 (5.88)          | 8 (6.78)               |            |         |

Values are presented as mean ± deviation or n (%). NIHSS – National Institute of Health Stroke Scale; GCS – Glasgow Coma Score; CMBs – cerebral microbleeds.
Table 4. Multivariate logistic regression analysis of significant risk factors for recurrent cerebrovascular events.

| Factor                  | OR   | 95%CI      | P value |
|-------------------------|------|------------|---------|
| Age                     | 1.071| 0.999–1.149| 0.055   |
| Silent cerebral infarction | 6.792| 1.631–28.28| 0.008   |
| C-reactive protein      | 0.854| 0.712–1.023| 0.086   |
| Urea                    | 0.655| 0.363–1.182| 0.160   |
| Leukoaraiosis           | 0.883| 0.420–1.856| 0.742   |

OR – odds ratio; CI – confidence interval; CMBs – cerebral microbleeds.

and other cardiovascular events. The results of our study were consistent with those of the above studies. The mechanism of increased risk of stroke or silent cerebral infarction due to increased WBC count is unclear, but it is presumed to be related to the process of atherosclerosis [25].

Logistic regression analysis showed that silent cerebral infarction in non-CAA ICH was an independent predictor of recurrent cerebrovascular events and related deaths during a follow-up period of 12 months. In our study, 22.37% of the patients experienced recurrent cerebrovascular events and related deaths. Kang et al. [3] also found that silent cerebral infarction occurring together with ICH increased the risk of future clinical cerebrovascular events or vascular deaths. Our findings are consistent with theirs. Therefore, a DWI scan after ICH can assess the risk of future clinical cerebrovascular events. Clinicians also need to pay attention to patients with silent cerebral infarction in ICH in order to reduce the incidence of clinical cerebrovascular events and vascular-related deaths.

This study had some limitations. All 152 patients had mild-to-moderate cerebral hemorrhage owing to the exclusion of patients with severe condition or who were undergoing surgery, which may have biased our results. Because of the strict criteria for inclusion into the group, the number of selected patients was relatively small and the follow-up time was short; thus, further studies with more cases and extended follow-up time are needed. Similar research should be carried out in CAA patients. Determining how to reduce the incidence of cardiovascular events in patients with silent cerebral infarction is also a promising research direction.

Conclusions

Silent cerebral infarction can occur in the acute phase of non-CAA ICH and is closely related to WBC counts, CMBs, and leukoaraiosis. A silent cerebral infarction following non-CAA ICH indicates a higher risk of clinical cerebrovascular events in the future.

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Conflicts of interest

None.

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