Original Contribution

Why Are Only Some Subcortical Ischemic Lesions on Diffusion Magnetic Resonance Imaging Associated With Stroke Symptoms in Small Vessel Disease?

Ophélie Osman, MD; François De Guio, PhD; Hugues Chabriat, MD, PhD; Eric Jouvent, MD, PhD

Background and Purpose—In cerebral small vessel diseases, small subcortical ischemic lesions (SSIL) on diffusion imaging are responsible for stroke manifestations but can also be occasionally observed in the absence of overt neurological symptoms. We aimed to determine, in a large cohort of young patients with CADASIL (Cerebral Autosomal-Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy), a severe monogenic condition leading to SSIL in young patients, the characteristics of SSIL and of surrounding cerebral tissue associated with the presence of stroke symptoms.

Methods—Among a cohort of 323 genetically confirmed CADASIL patients who were systematically evaluated every 18 months clinically and with magnetic resonance imaging, we studied all visible SSIL and documented ischemic stroke events with available magnetic resonance imaging data. We used mixed-effect logistic regression models to determine whether the presence of stroke symptoms was associated with age, sex, the volume of SSIL, their location with respect to preexisting white matter hyperintensities and with the load of the different magnetic resonance imaging markers of small vessel disease.

Results—We identified 73 SSIL (30 with stroke symptoms and 43 without) in 55 patients. In multivariable models, stroke symptoms were more frequent in male patients (estimate=1.94; SE=0.82; P=0.03) and less frequent when SSIL appeared in contact to preexisting white matter hyperintensities (estimate=−2.12; SE=0.83; P=0.01). Within pyramidal tracts, stroke symptoms were more frequent in patients with extensive white matter hyperintensities (estimate=3.8×10^{-5}; SE=9.3×10^{-6}; $P<10^{-4}$).

Conclusions—Altogether, our results suggest that when SSIL occur, the presence of stroke symptoms may depend on sex and alterations of the surrounding brain tissue rather than on the characteristics of the SSIL itself. (***Stroke*. 2018;49:00-00. DOI: 10.1161/STROKEAHA.118.021342.)**

Key Words: cerebral small vessel disease ■ ischemic stroke ■ lacune ■ magnetic resonance imaging ■ pyramidal tracts ■ white matter

Age- and hypertension-related cerebral small vessel diseases (sporadic SVDs) are responsible for 20% of all strokes.[1] In SVD, ischemic strokes are related to small subcortical ischemic lesions (SSIL), appearing in the first days as hyperintense lesions on diffusion-weighted sequences with a reduced apparent diffusion coefficient. Occasionally, SSIL can be observed in the absence of stroke symptoms when magnetic resonance imaging (MRI) is either systematically performed or prescribed for nonstroke symptoms such as headaches (Figure).

The occurrence of SSIL in eloquent brain areas such as the pyramidal tracts may of course explain why some lesions are associated with stroke symptoms.[2–5] Whether other mechanisms also influence the presence of stroke symptoms is by contrast undetermined. For instance, it has been shown that SSIL can evolve into white matter hyperintensities (WMH) or into cavitation,[6,7] but it is unknown if this aspect is associated with the presence of stroke symptoms. It has also been reported in a severe form of SVD that silent lacunes, presumably related to the cavitation of SSIL, appear preferentially in contact to preexisting WMH.[8] This has led the authors to hypothesize that WMH may represent a less functioning territory preventing SSIL to cause neurological deficits.

A systematic comparison of SSIL according to whether they are associated with stroke symptoms is hampered in sporadic SVD by the low expected incidence of SSIL without stroke symptoms. Also, in the absence of formal criteria to identify the underlying cause of SSIL, such an approach would likely be biased. For instance, the major source of SSIL not associated with stroke symptoms in the elderly is cerebral amyloid angiopathy, which is not a common cause of ischemic stroke.[9]

CADASIL (Cerebral Autosomal-Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy) is a severe monogenic form of SVD caused by mutations of the *NOTCH3* gene affecting young patients and characterized by

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From the Department of Neurology, APHP, Lariboisière Hospital, Paris, France (O.O., H.C., E.J.); University Paris Diderot, Sorbonne Paris Cité, UMR-S 1161 INSERM, France (O.O., F.D.G., H.C., E.J.); and DHU NeuroVasc Sorbonne Paris Cité, France (F.D.G., H.C., E.J.).

Correspondence to Eric Jouvent, MD, PhD, Hôpital Lariboisière, 2 Rue Ambroise Paré, 75010 Paris, France. Email eric.jouvent@aphp.fr

a high frequency of SSIL both associated or not with stroke symptoms.[10] Therefore, this pathology represents a unique opportunity to identify the main factors explaining why only some SSIL are associated with stroke symptoms.

Methods

Participants

We studied data from a prospective cohort of 323 CADASIL patients followed since 2003 in the French Referral Center for Rare Vascular Diseases of the Eye and the Brain (CERVCO, http://www.cervco.fr) in Lariboisière Hospital in Paris. Patients were included regardless of whether they had clinical manifestations of the disease, were at least 18 years of age, had a documented mutation of the *NOTCH3* gene, and were willing to be followed up. At inclusion and every 18 months thereafter, patients were evaluated by an experienced stroke physician and by a specialized neuropsychologist with a systematic neuropsychological battery including global cognitive evaluation through mini-mental state examination and Mattis Dementia Rating Scale, a verbal fluency test, the Grober & Buschke Free and Cued Selective Reminding Task, the similarity, block design and digit span subtests of the Wechsler Adult Intelligence Scale, revised version, as well as versions A and B of the trail making test, as previously reported.[11] Clinical, MRI, and biological data were collected at inclusion and each follow-up visit, as previously reported.[12] We identified from medical records all documented stroke events that happened during follow-up and for which clinical and MRI data were available. Given that patients originate from all areas of France, strokes were taken care of in local stroke units and patients were not evaluated at time of stroke in a systematic fashion. Given that up to 40% of CADASIL patients will not experience a stroke during their life,[10] we restricted our study to those who had a documented ischemic stroke. Indeed, we could not exclude that patients who will never experience any stroke during lifetime represent a specific disease subtype. Written informed consent was obtained from the study participants or a relative if the patient was too disabled. The study was approved by a local ethics committee.

Image Processing

Details of the MRI protocol have been previously reported.[13] All images were screened and processed by the same experienced reader blind to clinical data. All diffusion-weighted MRI data (planned MRI assessments and additional evaluations in case of ischemic stroke) were systematically screened for the presence of SSIL, which were defined as hyperintense lesions on diffusion-weighted sequences with a reduced apparent diffusion coefficient, with a maximum diameter of 2 cm, in line with the STRIVE criteria (Standards for Reporting Vascular Changes on Neuroimaging).[7] Multifocal lesions were excluded given that they may originate from specific context, including severe systemic hypotension.[14] Lacunes were defined as cavitated lesions of presumed ischemic origin and distinct from dilated perivascular spaces.[7]

Thereafter, SSIL were manually segmented with simple drawing tools using the Anatomist software (http://brainvisa.info). The segmentation procedure showed high intra- and interrater agreements (intraclass correlation coefficients of 0.98 and 0.88, respectively).

Thereafter, all lesion masks were registered to a common template (MNI152). We determined the anatomic location of SSIL according to the largest fiber bundles, in particular the pyramidal tracts, with the Johns Hopkins University white matter probabilistic tractography atlas.[15] In addition, masks were also registered to the more recent fluid attenuated inversion recovery sequence acquired before the occurrence of the SSIL to determine whether it occurred in contact or at distance from preexisting WMH. Whenever available, follow-up 3DT1 sequences were screened for the apparition of a cavity at the site of the SSIL. Cavitation was defined by a signal identical to that of the cerebrospinal fluid both on fluid attenuated inversion recovery and 3DT1 sequences.

For all patients, masks of WMH and of lacunes as well as the number of microbleeds were extracted with validated methods in agreement with the STRIVE criteria from fluid attenuated inversion recovery, 3DT1, and T2* sequences respectively, as previously detailed.[7] Although DTI acquisitions are part of our standard protocol, we did not use them in the present study. Indeed, we showed previously that DTI metrics are not comparable over long periods of time.[16] In addition, it is particularly difficult to reconstruct fiber tracts in patients with the largest lesion loads. In addition, for the largest tracts, like the pyramidal tract in the present case, probabilistic atlases represent a good enough approximation of the actual tracts.

Statistical Analysis

Characteristics of SSIL were compared according to whether they were associated or not with stroke symptoms. Given that several SSIL may have occurred in the same individual, group values are reported in Table but were not compared with conventional statistical test which would have yielded erroneous results. Actual group comparisons were performed in multivariable mixed-effect logistic regression models including a patient random effect to take into account multiple measures in some patients. We included as predictors the variables that could possibly influence the presence of stroke symptoms according to the literature: age, sex, the volume of SSIL, their occurrence at site of preexisting WMH, volumes of lacunes and of WMH, and number of microbleeds.

Given that the presence of stroke symptoms is likely influenced by the lesion site with respect to eloquent tracts, we performed additional analyses while restricting the analyses to SSIL occurring within the pyramidal tracts (defined according to the JHU probabilistic atlas). Additional analyses were performed in patients for whom data were available on cavitation.

This article adheres to the AHA Journals' implementation of the Transparency and Openness Promotion Guidelines. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Among the 323 patients of our cohort, 179 had a history of ischemic stroke at time of the present study. Among these, we identified 73 SSIL (30 SSIL with stroke symptoms and 43 SSIL without) in 55 patients. As stated in the Methods section, we did not perform classical statistical tests given that in some cases multiple SSIL were originating from the same individuals at different periods. A few parameters seemed

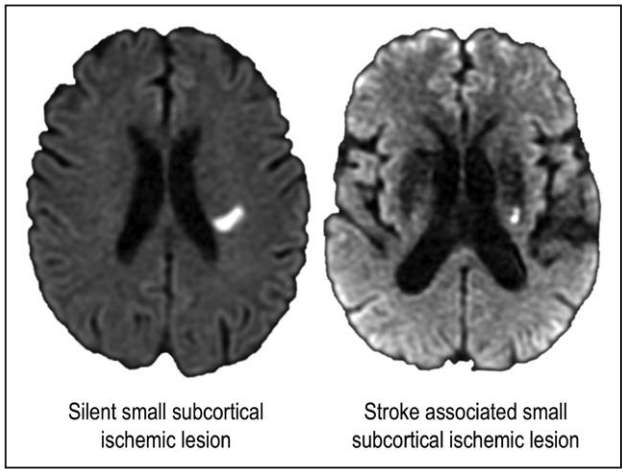

Figure. Recent small subcortical ischemic lesions on diffusion-weighted MRI. Example of 2 small subcortical ischemic lesions on diffusion-weighted magnetic resonance imaging (MRI) in 2 patients of our CADASIL (Cerebral Autosomal-Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy) cohort (**left**: discovered by chance on systematic follow-up MRI; **right**: ischemic stroke with motor involvement).

Table. Characteristics of SSIL Associated or Not With Stroke Symptoms

	SSIL With Stroke Symptoms (n=30)	SSIL Without Stroke Symptoms (n=43)
Age, mean±SD (range), y	59.5±8.6 (37.5–79.9)	56.6±9.4 (42.8–75.2)
Male sex, n (%)	13/30 (43)	22/43 (51)
Location in corticospinal tracts, n (%)	20/30 (66)	10/43 (23)
Lesion volume, mean, IQR (mm^3)	484.5, 354.1, 58.0–2649.0	292.7, 203.0, 38.7–2082.1
Preexisting WMH at contact of the site of SSIL, n (%)	9/24 (36)	28/40 (70)
Evolution toward cavitation on follow-up imaging, n (%)	14/20 (70)	19/23 (83)
Volume of WMH, mean, IQR (mm^3)	132 135, 81 781, 13 108–277331	120 601, 84 262, 21 344–256 465
Volume of lacunes, mean, IQR (mm^3)	1026, 748, 78–4472	1218, 1427, 70–3931
Presence of microbleeds, n (%)	21/30 (70)	29/43 (67)

IQR indicates interquartile range; SSIL, small subcortical ischemic lesion; and WMH, white matter hyperintensities.

anyway different between SSIL with stroke symptoms and SSIL without. Indeed, stroke symptoms seemed more frequent when SSIL occurred on pyramidal tracts (66% versus 23%) and when SSIL were larger (484.5 versus 292.7 mm^3). By contrast, stroke symptoms seemed less frequent when the SSIL occurred at site of preexisting WMH (36% versus 70%). The frequency of evolution toward cavitation appeared similar (70% in case of stroke symptoms versus 83% in absence of stroke symptoms), but this information was only available in 20 of 30 and 23 of 43 cases, respectively.

In mixed-effect logistic regression modeling, the presence of stroke symptoms was more frequent in male patients (estimate=1.99; SE=0.82; P=0.03), but less frequent when SSIL occurred in contact to preexisting WMH (estimate=−2.1; SE=0.83; P=0.01). By contrast, the presence of stroke symptoms was not associated with age, the volume of the SSIL, that of lacunes or of WMH, nor with the number of microbleeds.

When restricting the analyses to the 31 SSIL that occurred within pyramidal tracts, the presence of stroke symptoms was more frequent in patients with larger extents of WMH (estimate=0.006; SE=0.004; $P<10^{-4}$) and tended to be less frequent when SSIL occurred at site of preexisting WMH (estimate=−3.0; SE=1.72; P=0.08). By contrast, the presence of stroke symptoms was not associated, surprisingly, with the volume of the SSIL, nor with age, sex, the volume of lacunes, nor with the number of microbleeds.

Finally, in the 43 SSIL (20 SSIL with stroke symptoms and 23 SSIL without) for which cavitation could be studied on subsequent MRI acquisitions, the presence of stroke symptoms did not seem to be related to cavitation (estimate=−1.0; SE=2.2; P=0.62).

Discussion

In the present study of a large sample of young patients all affected by the same severe monogenic SVD, we found that stroke symptoms are more frequent in male patients but less frequent when SSIL occur at site of preexisting WMH. Surprisingly, even when restricting the analyses to SSIL occurring in pyramidal tracts, their size may not influence the presence of stroke symptoms, which were by contrast more frequent in patients with large extents of WMH. Altogether, our results suggest that preexisting alterations of surrounding brain tissue may be as important in determining the presence of stroke symptoms as the characteristics of the SSIL itself.

The reasons explaining why stroke symptoms are more likely to occur in male patients with SSIL remain to date undetermined. Although the disease is known to be more severe in male patients,[17] there are no or only mild relationships between ischemic strokes and disease severity in CADASIL.[12] The observed results might suggest the combination of 2 underlying processes. The white matter around sites of WMH may be less functional and less likely to lead to stroke symptoms, as previously suggested.[8] By contrast, SSIL occurring in the most severely diseased brains in male patients, in whom the white matter is globally altered, may be more likely to provoke neurological symptoms. In this respect, it may be worth highlighting that the influence of male sex on the presence of stroke symptoms was not significant when analyses were restricted to the pyramidal tracts. We could not exclude that we missed subtle differences in spatial distributions of SSIL outside the pyramidal tracts, associated with male sex, which may drive the observed association between male sex and stroke symptoms.

Although it is widely admitted that the occurrence of ischemic lesions in eloquent tracts is a major determinant of the presence of stroke symptoms, our results do not necessarily support this hypothesis. Indeed, we observed a significant number of SSIL without stroke symptoms in pyramidal tracts (23% of all SSIL without stroke symptoms). In addition, we did not find any relationship between SSIL volume and the presence of stroke symptoms in pyramidal tracts. By contrast, we found that lesions in pyramidal tracts were leading to stroke symptoms in patients having the largest burden of preexisting WMH.

A clear limitation of this study is that CADASIL is a rare disease and that our results may not be translatable to the general population. Also, we compared MRI performed on different scanners with different sensitivity to ischemic lesion detection. Nevertheless, we observed the same proportion of stroke symptoms in SSIL observed at 1.5 or at 3 T. In addition, the location of some lesions may be slightly imprecise because of spatial distortions inherent to diffusion-weighted MRI. Yet, acute ischemic lesions were mainly located in deep brain areas, only mildly affected by distortions. Also, we used an anatomic atlas instead of diffusion tensor imaging. Also, analyses were made

on a relatively small sample of ischemic lesions and we might have missed subtle cognitive or behavioral alterations leading to the erroneous classification of some SSIL in the without stroke symptom group. However, systematic evaluations that are performed every 18 months systematically comprise a clinical evaluation by an experienced stroke neurologist, a comprehensive neuropsychological assessment and MRI evaluation. The stroke neurologist, informed of the MRI result, systematically checked the absence of clinical symptoms (including subtle cognitive or behavioral changes) in the preceding 15 days. Finally, we chose to restrict our analyses to patients who already had a documented ischemic stroke at the time of the present study. Indeed, those who never experienced an ischemic stroke may represent a different disease subtype, which may have biased our results. In line, we systematically read the 359 MRI scans corresponding to the 144 patients who never experienced an ischemic stroke and only found 2 additional SSIL.

Altogether, our results suggest that sex and characteristics of the surrounding brain tissue influence the likelihood of the presence of stroke symptoms in relation with SSIL, further questioning the relevance of ischemic stroke as a clinical end point in SVD.

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Disclosures

None.

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