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## Magnetic resonance imaging characteristics of CADASIL

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## Subcortical lacunar lesions: an MR imaging finding in patients with CADASIL

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### **Abstract**

Purpose was to assess the prevalence and distribution of subcortical lacunar lesions (SLLs) in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), to determine whether SLLs are an abnormal finding by studying their prevalence in healthy subjects, and to assess whether SLLs occur in other conditions associated with small vessel disease and white matter areas of high signal intensity (WMHs).

The presence of SLLs, their location, and their relation to other abnormalities were assessed on magnetic resonance (MR) images (T1-weighted, T2-weighted, and fluid-attenuated inversion-recovery) obtained in 34 CADASIL patients and 20 healthy family members. Three additional control groups of healthy volunteers, elderly patients with vascular risk factors, and patients with another hereditary small vessel disease were also screened for the presence and location of SLLs. Sensitivity and specificity of the presence of SLLs for the diagnosis of CADASIL were assessed.

SLLs were found in 20 (59%) of CADASIL patients. Incidence of SLLs increased with age (20%, <30 years; 50%, 30–50 years; 80%, >50 years). SLLs invariably occurred in the anterior temporal lobes and in areas where diffuse WMHs expanded into arcuate fibers. From the anterior temporal lobe, the lesions could extend dorsally into the temporal lobes and rostrally into the frontal lobes. Lesions were not found in the parietal and occipital lobes. None of the control subjects had SLLs. Specificity and sensitivity of SLLs for CADASIL were 100% and 59%, respectively.

SLLs are an abnormal finding at MR imaging that frequently occur in CADASIL patients.

## **Introduction**

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary small artery vasculopathy caused by mutations in the *NOTCH3* gene on chromosome 19<sup>19,45,66</sup>. The disease is characterized clinically by transient ischemic attacks, strokes, progressive subcortical dementia, migraine with aura, and mood disturbances<sup>8,10,11</sup>. Pathologic examination of the brain demonstrates characteristic depositions of granular osmiophilic material within the media of the small and medium-sized leptomeningeal and long perforating arteries of the brain. The vasculopathy results in destruction of smooth muscle cells and fibrous thickening of the arterial wall<sup>7</sup>. Magnetic resonance (MR) imaging in patients with CADASIL typically reveals diffuse white matter areas with high signal intensity (WMHs) and lacunar infarcts in the centrum semiovale, thalamus, basal ganglia, and pons<sup>39-41</sup>. In symptomatic patients, MR images of the brain are always abnormal, but signal intensity abnormalities have also been detected in asymptomatic individuals who have the *NOTCH3* mutation<sup>45</sup>.

The diagnosis of CADASIL is confirmed by the demonstration of mutations in the *NOTCH3* gene; this confirmation process, however, is laborious because the *NOTCH3* gene is large, comprising 33 exons (i.e., distinct parts of genes which often encode discrete structural and functional units of proteins). Although 65% of known mutations occur in exons 3 and 4, the remaining exons must be screened, as well, in many cases. MR imaging plays an important role in the diagnostic work-up to increase the chance that CADASIL will be detected with genetic screening. It has recently been demonstrated that CADASIL can be differentiated from Binswanger's disease at MR imaging, but differentiation of CADASIL from other diseases that can be associated with white matter abnormalities is unclear<sup>67</sup>. Therefore, the discovery of more specific neuroimaging features of CADASIL might help increase the chance of identifying CADASIL patients.

Recently, we reviewed brain MR imaging studies of members of families with CADASIL as part of a study on the clinical, radiologic, and genetic aspects of CADASIL in the Netherlands. During this study, we observed a pattern of subcortical lacunar lesions (SLLs) in patients with CADASIL that, to the best of our knowledge, has not been previously described. The aim of the present study was threefold: to assess the prevalence and distribution of SLLs in CADASIL patients, to determine whether SLLs are an abnormal finding by studying their prevalence in a control series of healthy subjects from the general population, and to assess whether SLLs occur in other conditions that are associated with small vessel disease and WMHs.

### **Materials and methods**

Members of 15 unrelated Dutch families with CADASIL were asked to participate in a study on the clinical, radiologic, and genetic aspects of CADASIL. In each family, the index patient had a proven pathogenic *NOTCH3* mutation. Patients were referred from various medical centres to our institution, which serves as a CADASIL referral centre. Patients were referred because they were suspected of having CADASIL on the basis of clinical signs and symptoms, a family history consistent with autosomal dominant inherited disease, or suggestive changes at MR imaging such as WMHs and lacunar infarcts. The presence of SLLs was never the reason for referral. At our institution, the diagnosis of CADASIL was confirmed with direct sequencing analysis of the *NOTCH3* gene according to previously described techniques<sup>22</sup>. Thirty-four patients formed the group in our study.

The following four control groups were used:

1. Members of CADASIL families without the *NOTCH3* mutation.
2. A group of 75 adult subjects (<65 years of age) who were randomly recruited from the general population, did not have abnormalities at standard neurologic examination, and had no history of cardiovascular events.

These two groups served to assess whether SLLs occur in evidently healthy individuals.

To assess whether SLLs occur in patients with other conditions that are associated with small vessel disease and WMHs, we studied two additional control groups:

3. A group of 16 age-matched patients with DNA-proven hereditary cerebral haemorrhage with amyloidosis–Dutch type (HCHWA-D). HCHWA-D is an autosomal dominant small vessel disease of the brain caused by  $\beta$ -amyloid depositions in cerebral arterioles and leptomeningeal arteries that is associated with extensive supratentorial WMHs<sup>68-70</sup>.
4. A group of 75 elderly subjects (>70 years) from the general population with an increased risk of having cerebral WMHs because they had cardiovascular disease or at least one major vascular risk factor (hypertension, cigarette smoking, or diabetes mellitus; for criteria see reference 16). These subjects were randomly selected from a larger study group that had participated in a randomized controlled trial investigating the effect of cholesterol-lowering treatment with pravastatin on cardiovascular disease and stroke. All subjects were imaged at baseline<sup>71</sup>.

The patients in all control groups underwent the same MR imaging protocol as the patients with CADASIL. Only cognitively capable subjects were included in this study to ensure informed consent. The medical ethics committee of

our institution approved the protocol of our entire study. Informed consent was obtained from all subjects in each of the four control groups and from all subjects in the CADASIL group.

All MR imaging examinations were performed with a 1.5-T MR system (Philips Medical Systems, Best, the Netherlands) between August 1999 and June 2001. Conventional T1-weighted spin-echo images (section thickness, 6 mm; intersection gap, 0.6 mm; repetition time msec/echo time msec, 600/20; matrix, 256 x 205; field of view, 220 x 165 mm), dual T2-weighted fast spin-echo images (section thickness, 3 mm; no intersection gap; 3000/27, 120; matrix, 256 x 205; field of view, 220 x 220 mm), and fast fluid-attenuated inversion-recovery (FLAIR) images (section thickness, 3 mm; no intersection gap; repetition time msec/echo time msec/inversion time msec, 8000/100/2000; matrix, 256 x 192; field of view, 220 x 176 mm) were obtained. To detect haemosiderin deposits, we performed a T2\*-weighted gradient-echo pulse (echo-planar imaging [EPI]) sequence (section thickness, 6 mm; intersection gap, 0.6 mm; 2598/48; matrix, 256 x 192; field of view, 220 x 198 mm; EPI, 25). All sequences were performed in the axial plane parallel to the inferior border of the genu and splenium of the corpus callosum.

SLLs were defined as linearly arranged groups of rounded, circumscribed lesions just below the cortex at the junction of the grey and white matter with a signal intensity that was identical to that of cerebrospinal fluid (CSF) on images obtained with all pulse sequences. On each section of the brain, the following aspects of SLLs were assessed: anatomic location, distribution, bilaterality, size, and relation to other abnormalities such as WMHs and haemosiderin deposits. With the validated visual rating score of Scheltens et al, deep white matter lesions were rated on the basis of film hard copies of FLAIR MR images<sup>59</sup>. A Scheltens score of deep WMHs of 1 or more was considered to indicate presence of WMHs, while a score of 0 implied absence of deep WMHs. When SLLs were visible, the presence of haemosiderin deposits in the vicinity of the SLLs was recorded on the basis of T2\*-weighted gradient-echo MR images. In addition, prevalence of SLLs in the groups of CADASIL patients and control subjects was assessed. Finally, in CADASIL patients, prevalence of SLLs was established in male and female patients separately, and the relationship between SLLs and age was established. All MR images were reviewed by the same neuroradiologist (MAvB) who was blinded to clinical and genetic data.

During this study, we reviewed histologic information about any subject participating in the study in whom this information might be available. In one patient who died and in whom we found SLLs before death, we had the opportunity to investigate formalin-fixed tissue of the anterior temporal lobe (tissue was investigated with permission of the family and was kindly

supplied by Frits F.J.M. Sutorius, MD, Stichting Laboratorium Pathologie Oost Nederland, Enschede, the Netherlands). Tissue was embedded in paraffin, and haematoxylin-eosin and Klüver-Barrera stains were used.

Descriptive statistics were calculated for differences in age and sex and for the presence of SLLs in various areas of the brain. The sensitivity and specificity of the presence of SLLs for the diagnosis of CADASIL were calculated by comparing data from CADASIL patients with data from the elderly subjects and from the HCHWA-D patients. Comparisons after grouping subjects by age (i.e., <30 years, 30–50 years, and >50 years) were assessed with the Fisher exact test. Values of  $P < 0.05$  were considered to represent a statistically significant difference. The statistical analysis was performed with SPSS-10 software (SPSS, Chicago, Ill).

## Results

The total number of participants from families with CADASIL was 54. Thirty-four participants had a mutation in the *NOTCH3* gene and 20 did not (for group characteristics, see table 1). In the majority of *NOTCH3* mutation carriers, the mutation was located in exon 4; in the remaining patients, it was located in exon 8, 19, or 20. Twenty-six mutation carriers were symptomatic; eight were asymptomatic. The group of mutation carriers included 17 women and 17 men, with a mean age of 45 years  $\pm$  12 (SD) and 46 years  $\pm$  11, respectively. In all CADASIL patients, deep WMHs were present. Eight (40%) of the CADASIL family members without mutations, 44 (59%) of the normal adults, 11 (69%) of the HCHWA-D patients, and 64 (85%) of the elderly patients with vascular risk factors had deep WMHs.

Table 1 Characteristics of study groups

Study group	No. of subjects	Age (y)		Sex		No. of SLLs
		Mean $\pm$ SD	Range	Men	women	
CADASIL patients	34	46 $\pm$ 11	21-60	17	17	20
CADASIL family members without mutation	20	40 $\pm$ 13	22-67	8	12	0
Healthy control subjects	75	48 $\pm$ 8	34-62	24	51	0
Elderly with vascular risk factors	75	78 $\pm$ 3	72-85	56	19	0
HCHWA-D patients	16	48 $\pm$ 9	34-63	10	6	0

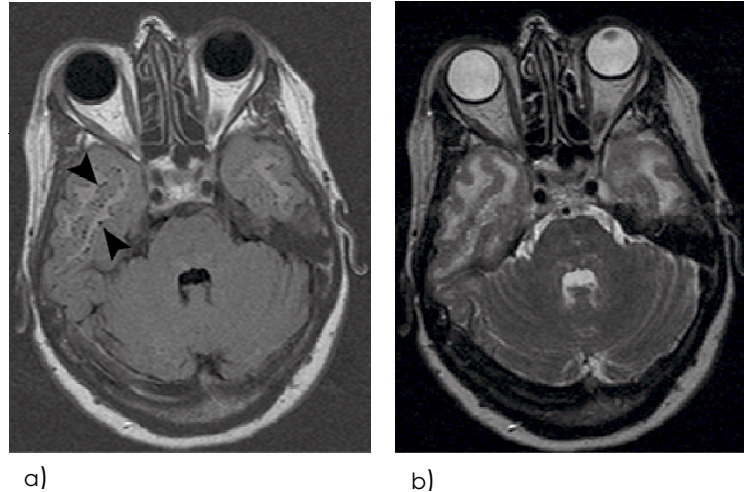


Figure 1 Axial MR images in patient with CADASIL at the level of the pons. Hyperintense confluent white matter lesions in the temporal lobe are visible on (a) a FLAIR image and a (b) T2-weighted image. On the FLAIR image, the SLLs (arrowheads) are clearly visible on the T2-weighted image they hardly be discriminated from the adjacent WMHs.

Because of the high contrast between SLLs and WMHs on FLAIR MR images, SLLs were detected only on these images. Therefore, the results given next are based on the visibility of SLLs on FLAIR MR images. SLLs were found in 20 of 34 CADASIL patients (59%; mean age, 49 years  $\pm$  8) (table 1). The signal intensity of SLLs was equivalent to that of CSF on images obtained with all pulse sequences. The low contrast between these lesions and the abutting confluent areas with low signal intensity on T1-weighted images and high signal intensity on T2-weighted images lessened the visibility of SLLs with these sequences (figure 1). None of the four control groups had SLLs (table 1). Specificity and sensitivity of the presence of SLLs in CADASIL were 100% (95% CI: 98, 100) and 59% (95% CI: 41, 75), respectively (table 2). SLLs were found in one (20%) of five patients less than 30 years of age, in seven (50%) of 14 patients 30–50 years of age, and in 12 (80%) of 15 patients more than 50 years of age. The difference in prevalence of SLLs between these three age groups was significant ( $P < 0.05$ ). SLLs were more prevalent in male CADASIL patients: Eight female (47% of all women) versus 12 male (71% of all men) patients were affected, but the difference was not significant ( $P > 0.05$ ). When SLLs were present, they were numerous, their size varied between 1 and 2 mm, and they occurred in all cases in the temporopolar part of the brain (defined as the part anterior to the temporal horns<sup>67</sup>). In four patients, the lesions expanded from this anterior location posteriorly and affected the entire temporal lobe (figures 2a, 2b). In five patients (25%), SLLs were also located in the operculum of the frontal lobe (figure 2c). In one patient with extensive white matter

lesions, SLLs were visible throughout the whole temporal and frontal lobes (figure 2d). SLLs were never observed in the parietal and occipital lobes or infratentorially. The lesions had a symmetric distribution in 85% of patients; in 15% of patients, SLLs occurred unilaterally. SLLs invariably abutted white matter areas, with confluent areas of high signal intensity on FLAIR MR images. They were never found in juxtaposition to white matter with a normal appearance on images obtained with this sequence. The surface of the SLLs that abutted the cortical ribbon did not show signal intensity abnormalities. No evidence of haemosiderin deposits was found in the vicinity of the lesions.

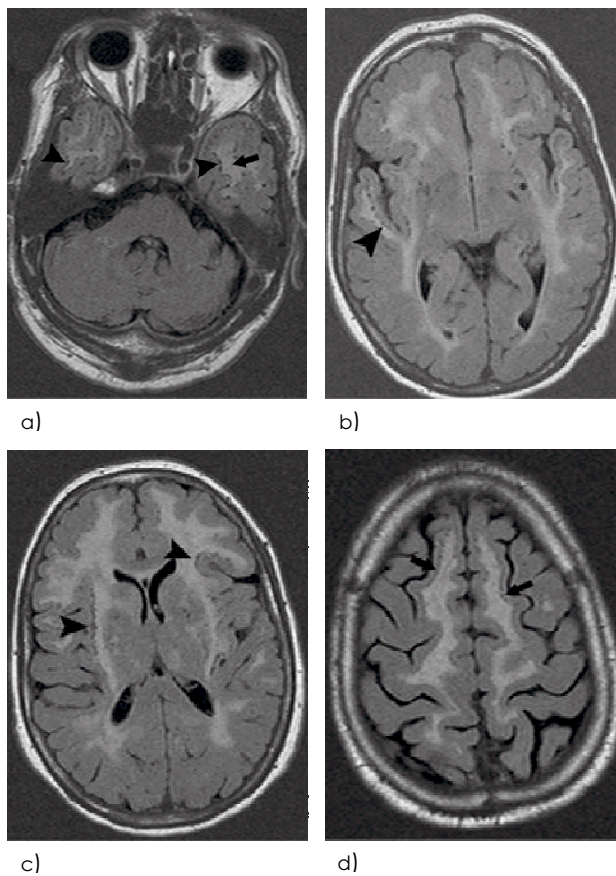


Figure 2 Axial FLAIR MR images in four CADASIL patients at the level of (a) the pons, (b) the operculum of the temporal lobe, (c) the basal ganglia, and (d) the high convexity. Images show bilateral SLLs affecting a) the anterior part and (b) the operculum of the temporal lobe (arrowheads) at the junction of grey and white matter. The lesions are abutting WMHs (arrow in a). From this location, lesions could expand to (c) the subinsular region and operculum of the frontal lobe (arrowheads). (d) In one patient with extensive white matter lesions, subcortical lacunar lesions were visible throughout the whole frontal lobe (arrows).

Histologic examination of the tissue sections of the anterior temporal lobe from one patient revealed vascular changes characteristic of CADASIL<sup>7</sup>. Furthermore, when slides were viewed macroscopically, they showed in several areas a typical periodicity of lacunae perpendicular to the border of the grey and white matter. This phenomenon was caused microscopically by a clear zone around perforating vessels (figure 3b). These vessels occasionally showed a thickened wall with granular material but often lacked obvious changes. The clear zone consisted of a distended perivascular space, which often contained some haemosiderin, and spongiosis (oedema) of the adjacent parenchyma (figure 3c). A row of several of these periodically arranged lacunae represent the substrate for the linear lesions observed at MR imaging (figure 3a).

*Table 2 Visibility of SLLs on FLAIR MR Images in the CADASIL group and in two other groups with conditions associated with small vessel disease and WMHs (elderly patients with vascular risk factors and patients with HCHWA-D)*

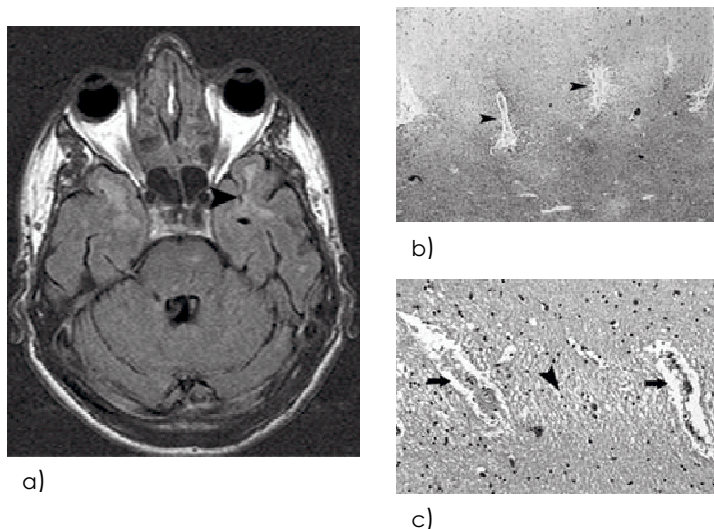
SLLs status	CADASIL patients	Elderly and HCHWA-D patients (n = 91)
Present	20	0
Absent	14	91
Total	34	91

*Note: The finding of SLLs on FLAIR MR Images has a sensitivity of 59% and a specificity of 100% for the diagnosis of CADASIL.*

## **Discussion**

In this article, we describe a type of lacunar lesion that, to our knowledge, has not been previously described in the neuroimaging literature in either patients with CADASIL or patients with other disorders. Microscopic examination reveals that the lacunae are caused by a distention of the perivascular space of perforating arteries at the level of the junction of grey and white matter and by spongiosis in the surrounding parenchyma. The observed widened perivascular space, which is known to contain CSF, provides an explanation for the observation in our study that the signal intensity of SLLs at MR imaging was equivalent to that of CSF. Furthermore, the presence of spongiosis in the surrounding parenchyma may explain the confluent aspect of SLLs that is frequently found at MR imaging. The abnormalities we found microscopically have a strong resemblance to the laminar lacunar lesions between the cortical ribbon and the subcortical white matter that have been described by Ruchoux et al in a post-mortem study of a patient with CADASIL<sup>34</sup>. The

presence of spongiosis and haemosiderin in the surrounding parenchyma suggests local damage to the blood-brain barrier at the junction of grey and white matter in perforating arteries.



*Figure 3 Axial FLAIR MR image (a) in a patient with CADASIL in whom we obtained formalin-fixed tissue of the anterior temporal lobe after death. Subcortical lacunar lesions are present in the temporal lobe (arrowhead). Photomicrograph (b) shows a row of perforating vessels at the border of grey matter (top of image) and white matter with an obvious clear zone (arrowheads). (Klüver-Barrera stain; original magnification, x20.) Photomicrograph (c) shows detail of two vessels. The lower part of the vessel on the left shows characteristic thickening of the arterial wall; both vessels have a distended perivascular space (arrows) and spongiosis of the adjacent parenchyma (arrowhead). (Haematoxylin-eosin stain; original magnification, x100.*

Despite the histologic similarity of SLLs to dilated perivascular or Virchow-Robin spaces, it is possible to distinguish SLLs from otherwise widened Virchow-Robin spaces on MR images based on their location. At MR imaging, widened Virchow-Robin spaces are often seen in healthy individuals in the deep white matter of the high convexity, at the base of the brain adjacent to the anterior or posterior surface of the lateral portion of the anterior commissure, in the midbrain, and in the subinsular white matter<sup>72</sup>. SLLs cannot be confused with Virchow-Robin spaces in the white matter of the high convexity, at the base of the brain, and in the midbrain because (a) SLLs occur only at the subcortical junction of the grey and white matter and (b) the sites of predilection of SLLs are the anterior, temporal, and frontal lobes, where Virchow-Robin spaces are not usually found in healthy individuals. SLLs with a subinsular location could be confused with Virchow-Robin spaces because of their location. However, unlike Virchow-Robin spaces, SLLs appear only in the presence of WMHs, are always accompanied by SLLs in the anterior temporal lobe, and do not have the featherlike appearance that is characteristic of Virchow-Robin spaces in

this location<sup>73</sup>. In addition to being confused with Virchow-Robin spaces, SLLs can also be confused with normal variations in the temporal lobe. Hippocampal sulcus remnants are apparent at MR imaging as small circumscribed areas with a signal intensity similar to that of CSF in the hippocampus<sup>74</sup>. These structures can be differentiated from SLLs by their location because hippocampal sulcus remnants occur within the hippocampus and are surrounded by hippocampal grey matter, whereas SLLs are seen only at the cortical junction of grey and white matter. Furthermore, contrary to hippocampal sulcus remnants, SLLs will never appear only in this region; they are always accompanied by SLLs in the anterior part of the temporal lobe.

In this study, we observed SLLs in the temporal lobes and to a lesser extent in the frontal lobes. Within the temporal lobes, the anterior (temporopolar) part was a site of predilection for SLLs; this area was invariably affected in patients with SLLs. This distribution pattern of SLLs closely resembles the pattern of WMHs in CADASIL patients that has recently been described. Both Auer et al and O'Sullivan et al demonstrated that temporal pole WMHs are a characteristic finding of CADASIL, which enables the differentiation of CADASIL from Binswanger's disease<sup>43,67</sup>. In addition, Auer et al demonstrated that expansion of WMHs into the arcuate fibers is typical of CADASIL; this finding further helps in differentiating CADASIL from Binswanger's disease<sup>67</sup>. In addition to this similarity in distribution of SLLs and WMHs, in our study, SLLs were always observed to be abutting WMHs that had expanded into the subcortical arcuate fibers. The similarity in distribution of SLLs and WMHs and their invariable side-by-side occurrence suggests that they have the same pathogenesis. Both phenomena probably result from local degeneration of the perforating arteries at the level of the cortical junction of grey and white matter. The observation that SLLs were never found without WMHs expanding into arcuate fibers, whereas such WMHs lesions were found without SLLs, suggests that WMHs precede the occurrence of SLLs and that SLLs are a manifestation of more advanced disease than are WMHs.

Although SLLs were found in the majority of patients with CADASIL in our study, to our knowledge, the presence of SLLs has not been reported in the numerous previously published articles on neuroimaging findings in patients with CADASIL. This discrepancy between our and other imaging studies might be explained by our use of FLAIR MR images with thin sections (3 mm). In most previous MR imaging studies of CADASIL, only T1- and T2-weighted MR images were used for detecting brain lesions<sup>39-41</sup>. On T1- and T2-weighted images, SLLs are hard to detect because both SLLs and WMHs have low signal intensities on T1-weighted images and high signal intensities on T2-weighted images. The similar signal intensities and the existence of SLLs and WMHs in close proximity make it hard to detect the subtle SLLs at the border of the

larger and more obvious confluent WMHs. However, on FLAIR images, a high contrast is generated between SLLs and WMHs. On FLAIR images, the signal intensity of CSF is selectively suppressed, rendering CSF and CSF-filled structures black, whereas the high signal intensity of most pathologic changes of brain parenchyma is maintained. Because of this high contrast, the CSF-filled SLLs are clearly visible on FLAIR MR images as black lesions between the grey cortex and the WMHs. Because SLLs are small, they are more visible when thin sections are used.

In conclusion, SLLs are a previously unreported imaging finding in patients with CADASIL. In this study, SLLs were found in 59% of patients with CADASIL; this suggests that SLLs are characteristic of the disease. SLLs were not found in healthy control subjects, which suggests that SLLs are not a normal condition like the physiologic Virchow-Robin spaces that are often detected at MR imaging in healthy individuals. SLLs were not found in two other populations with a high prevalence of WMHs induced by small vessel disease. This suggests that SLLs might be specific for CADASIL, and that detection of their presence may help to narrow the differential diagnosis and even establish the diagnosis in patients with WMHs. Further studies of the occurrence of SLLs in other cerebral diseases are needed to assess the specificity of SLLs for CADASIL.