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## Magnetic resonance imaging characteristics of CADASIL

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Radiological distinction between  
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# Radiological distinction between patients with CADASIL and MS

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*Submitted Radiology*

## **Abstract**

Purpose was to study whether there is a difference in magnetic resonance (MR) lesion pattern between young patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and multiple sclerosis (MS).

The presence of lacunar infarcts, microbleeds, subcortical lacunar lesions, and white matter hyperintensities (WMHs) in the anterior temporal lobe and the external and internal capsule was assessed on MR images. Images were obtained in 24 CADASIL patients and 19 MS patients under the age of 50 years, comprising T1-weighted, dual fast spin-echo, fluid attenuated inversion recovery (FLAIR), and T2\*-gradient-echo images in the axial plane. Differences were assessed with the Fisher's exact test.

CADASIL patients showed significantly more subcortical lacunar lesions, lacunar infarcts, and hyperintensities in the anterior temporal lobe and the external capsule compared with MS. The presence of WMHs in the internal capsule and microbleeds did not differ significantly between the patient groups.

Based on the presence and pattern of abnormalities observed on MR images of CADASIL patients, young CADASIL patients can be discriminated from young patients with MS.

## **Introduction**

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is a late-onset hereditary syndrome caused by mutations in the *NOTCH3* gene<sup>19</sup>. The pathological substrate is a microangiopathy characterized by distinctive granular osmiophilic material in the vascular media, leading to degeneration of vascular smooth muscle cells<sup>7</sup>. The disease is clinically characterized by initially attacks of migraine with aura (<age 30) and later on (>age 40) transient ischemic attacks, strokes, progressive subcortical dementia, and mood disturbances<sup>8</sup>. The radiological hallmarks of CADASIL are the presence on magnetic resonance (MR) imaging of white matter hyperintensities (WMHs) with a specific distribution, and lacunar infarcts, subcortical lacunar lesions, and microbleeds<sup>39-41,43,76,77,92</sup>. Recently we described that these lesions develop in a predictable way during the course of the disease<sup>78</sup>. As early as in the third decade of life subcortical lacunar lesions and patchy WMHs usually located in the anterior temporal lobe can be found whereas in the sixth decade a full-blown picture with confluent WMHs, subcortical lacunar lesions, lacunar infarcts, and microbleeds is observed in most patients.

Whereas the radiological picture of advanced stages of CADASIL is well documented, and can usually be discriminated from Binswanger's disease, the radiological appearance at earlier stages of CADASIL may mainly comprise only of WMHs, similar to those found in multiple sclerosis (MS)<sup>67</sup>. As MS may also have a similar clinical presentation as CADASIL many CADASIL patients are misdiagnosed as MS<sup>49,50</sup>. Here we compared the cerebral MR pictures of relatively young CADASIL patients with those of age-matched MS patients in order to identify radiological features that may help to discriminate CADASIL already at the early stages from MS.

## **Materials and methods**

### **Subjects**

We included 24 patients (<50 years) with proven *NOTCH3* mutations from 15 unrelated Dutch CADASIL families, participating in our ongoing prospective study on clinical, radiological and genetic aspects of CADASIL<sup>22</sup>. These patients were compared with 19 age-matched patients with laboratory-supported definite MS who were recruited from the authors' institution<sup>99</sup>. Only subjects who were able to understand the informed consent were included and informed consent was obtained from all subjects. The medical ethics committee of our institution approved the study protocol.

### **MR imaging**

All MR examinations were performed on a 1.5T MR system (Philips Medical systems, Best, The Netherlands). All participants were subjected to the same standardized MR protocol, comprising: conventional T1-weighted spin echo images (slice thickness 6 mm with a 0.6 mm interslice gap [6.0/0.6 mm], repetition time [TR]/echo time [TE] 600/20 ms, matrix 256x205, and a 220x165 mm field of view [FOV]), dual T2-weighted fast spin echo (FSE) images (3.0/0.0 mm, TR/TE 3000/27/120 ms, matrix 256x205, FOV 220x220 mm), and fast fluid-attenuated inversion recovery (FLAIR) images (3.0/0.0 mm, TR/TE 8000/100 ms, inversion time 2000 ms, matrix 256x192, FOV 220x176 mm). In addition, T2\*-weighted gradient echo planar (EPI) sequence (6.0/0.6 mm, TR/TE 2598/48 ms, matrix 256x192, FOV 220x198 mm, EPI factor 25) were performed to detect haemosiderin deposits. All images were performed in the axial plane parallel to the inferior border of the genu and splenium of the corpus callosum.

### **Visual rating**

Two radiologists (MAvB, RvdB) blinded to the diagnosis of CADASIL and MS assessed for each patient the presence of the radiological hallmarks of CADASIL: lacunar infarcts, microbleeds, subcortical lacunar lesions, and WMHs in the anterior temporal lobe, the external and internal capsule.

Lacunar infarcts were defined as parenchymal defects not extending to the cortical grey matter with a signal intensity following that of cerebral spinal fluid (CSF) on all pulse sequences, irrespective of size (figure 1). In an effort to differentiate lacunar infarcts from dilated perivascular spaces, areas that were isointense to CSF on all pulse sequence and located in the lower one-third of the corpus striatum, were excluded<sup>80,100</sup>. Subinsular perivascular spaces were differentiated from lacunar infarcts based on the description of Song et al: enlarged perivascular spaces have a featherlike configuration, are isointense to CSF on T2- and T1-weighted images, but do not have high signal on FLAIR images<sup>73</sup>. In an effort to differentiate perivascular spaces along the perforating arteries from lacunar infarcts a modification of the descriptive criteria for perivascular spaces as used by Bokura et al was applied: all lesions with a transverse diameter smaller or equal to 2 mm or with a tubular appearance following the course of perforating arteries were most likely to represent perivascular spaces and were excluded as well<sup>61</sup>.

Microbleeds were defined as focal areas of signal loss on T2-weighted FSE images that increased in size on the T2\*-weighted gradient echo pulse sequence ("blooming effect") (figure 1)<sup>76</sup>. In this way, microbleeds were differentiated from areas of signal loss based on vascular flow voids. Areas of symmetric hypointensity of the globus pallidus likely to represent calcification or nonhemorrhagic iron deposits were excluded.

Subcortical lacunar lesions were defined as linearly arranged groups of rounded, circumscribed lesions just below the cortex, at the grey-white matter junction with a signal intensity that was identical to that of CSF on all pulse sequences (figure1)<sup>92</sup>.

WMHs were defined as white matter areas with increased signal intensity on dual and FLAIR weighted images without mass effect. The border between anterior and posterior temporal lobe was defined as the posterior margin of the amygdale (figure1)<sup>43</sup>.

### **Group comparison with automated statistical image analysis tool**

WMH volume (in ml) measurements were performed using locally developed automated segmentation software (Sniper®, Department of Radiology, Division of Image Processing, Leiden University Medical Centre, Leiden, The Netherlands). Volume of WMHs was corrected for total brain volume by dividing the individual volume of WMHs by intracranial volume and expressed in percent. WMHs detection approach consisted of three main steps:

1. Brain stripping: An average proton density image (from the Montreal Neurological Institute (MNI)) is first co-registered to the proton density image of a subject using a multi-resolution 12-parameter affine registration. The standard deviation of ratio images was used as cost function. The resulting transformation matrix is used to resize an intracranial prior probability map in order to mask automatically non-brain voxels (skin, bone and eyeballs). A prior probability map of white matter (from MNI) is aligned using the same transformation matrix to guide the detection of the WMHs. For a more accurate intracranial delineation, fuzzy clustering, mathematical morphology and region growing, are applied and constraint to remain within the resliced intracranial mask. This step takes on average less than 1 minute per scan.
2. CSF detection: The FLAIR image is first co-registered to the T2-weighted image. A ratio image (FLAIR/T2) is then computed after rescaling the FLAIR voxel-intensity range to that of the T2-weighted image. The CSF is extracted in this ratio image using fuzzy clustering ( $c=2$ ). The voxels belonging to the cluster with the darkest signal intensities within the intracranial mask are classified as CSF.
3. Lesion detection: The voxels of the T2-weighted image and those of the FLAIR image are clustered in 3 clusters. A voxel is labelled as WMH if it fulfils three conditions: (i) Its T2 intensity belongs to the brightest cluster and it does not intersect with the CSF mask detected in step 2; (ii) its FLAIR intensity belongs to the brightest cluster; (iii) it has a relatively high probability ( $>0.4$ ) to belong to the white matter (using the aligned white matter map). Finally figure 2 shows at the level of the anterior temporal lobe and the external and internal capsule for every voxel whether WMHs were present at these

locations, in blue for CADASIL, in red for MS. The brighter the colour the more frequently WMHs were found in that location. As background we used a normalized T1-weighted image.

### **Statistical analysis**

Descriptive statistics were calculated for differences in age and sex between CADASIL and MS patients. Differences in presence of subcortical lacunar lesions, lacunar infarcts, microbleeds and hyperintensities in the anterior temporal lobe, the external and internal capsule between CADASIL and MS patients were assessed with the Fisher's exact test. Differences in WMH volume was assessed with a Student t-test for unpaired data. To compensate for multiple comparisons, we considered a P-value of  $P < 0.005$  as significant. The agreement between the two readers was determined with Cohen's K. The statistical package SPSS-10 (SPSS, Inc) was used for data analysis.

*Table 1 Characteristics of the CADASIL and MS patients*

Study group	Subjects (n)	Age (y)		Sex (n)	
		Mean $\pm$ SD	Range	Men	Women
CADASIL	24	40 $\pm$ 10	21-50	10	14
MS	19	42 $\pm$ 9	26-53	4	15

*Table 2 Presence of MR lesions in CADASIL and MS patients*

	CADASIL (n=24)	MS (n=19)	P value
Subcortical lacunar infarcts (n)	9	0	0.002*
Lacunar infarcts (n)	15	0	<0.001*
Microbleeds (n)	4	0	0.12*
Anterior temporal lobe (n)	23	1	<0.001*
External capsule (n)	14	0	<0.001*
Internal capsule (n)	15	1	0.04*
Volume of WMHs (mean %)	4.5%	0.7%	<0.001**

\*Fischer exact test

\*\* Student t-test

## Results

### Subjects

Table 1 gives an overview of the characteristics of the CADASIL and MS patients. There were no significant differences in age (Student-t test,  $P=0.57$ ) and sex (Fisher's exact,  $P=0.20$ ) between CADASIL and MS patients.

### Visual rating

The interobserver agreement was high for all MR imaging abnormalities ( $\text{Kappa}=0.88-1$ ). The presence of subcortical lacunar lesions, lacunar infarcts, microbleeds and hyperintensities in the anterior temporal lobe, the external and internal capsule in CADASIL and MS patients are given in table 2. The following radiological features were significantly higher in patients with CADASIL compared with those with MS (Fisher's exact test,  $P<0.005$ ): subcortical lacunar lesions, lacunar infarcts, and hyperintensities in the anterior temporal lobe and the external capsule (table 2). Although microbleeds were absent in MS patients, only four CADASIL patients had microbleeds and therefore no statistically difference was found between the two diseases. There was one MS patient with hyperintensities in the internal capsule. In CADASIL, WMHs in the internal capsule were seen in 15 patients. This radiological hallmark also did not reach significance.

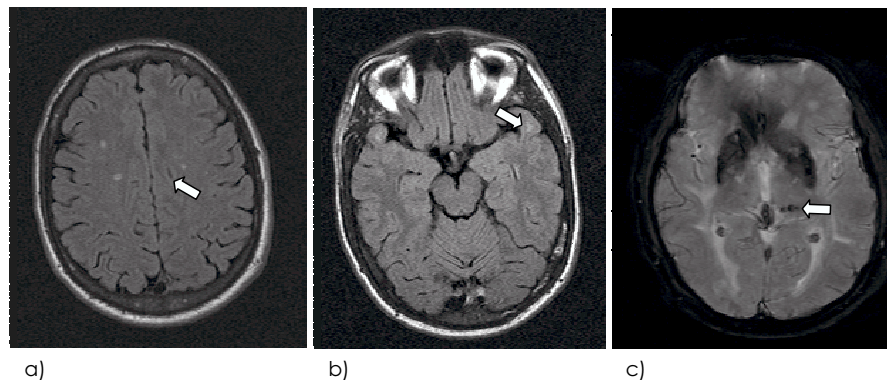


Figure 1 Axial FLAIR (a-b) and T2\*-weighted (c) MR images of CADASIL patients. Complete MR spectrum of CADASIL: lacunar infarcts (arrow in a), subcortical lacunar lesions (arrow in b) and microbleeds (arrow in c).

### Group comparison with automated statistical image analysis tool

As shown in figure 2, there is a difference in WMHs distribution between CADASIL and MS patients. Also, the volume of WMHs, corrected for intracranial volume was significantly higher in CADASIL (mean 4.5%, SD 3.7) as compared with MS patients (mean 0.7%, SD 1.1, Student t-test,  $P<0.001$ , table 2).

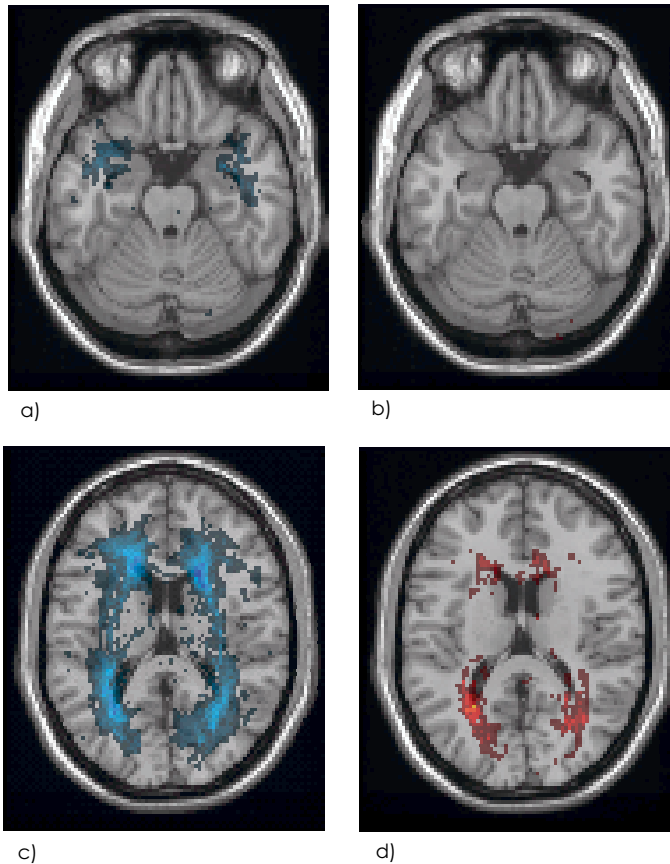


Figure 2 Frequency maps of the distribution of WMHs generated with automated statistical image analysis tool. Areas where WMHs occurred are displayed in colour; the brighter the colour, the higher the frequency of WMHs in these locations. The distribution of the WMHs in the CADASIL group is shown left (a and c) and in the MS group right (b and d) at the level of the anterior temporal lobe (a and b) and the external and internal capsule (c and d). Almost no WMHs were seen in the anterior temporal lobe, and internal and external capsule in MS patients whereas WMHs were more often present in these locations in the CADASIL population.

### Discussion

We compared brain MR images of young patients with CADASIL with those of patients with MS and found significant differences with respect to the volume and distribution of WMHs and the presence of concomitant lesions. MR images of young CADASIL patients revealed a significantly higher load of WMHs and a characteristically higher prevalence of WMHs in the anterior temporal lobe (23/24 in CADASIL versus 1/19 in MS) and the external and internal capsule (14-15/24 in CADASIL versus 0-1/19 in MS). The results show that involvement

of the anterior temporal lobe is not only a useful radiological hallmark to differentiate CADASIL from Binswanger's disease in elderly patients but also to differentiate CADASIL from MS in younger patients<sup>67</sup>.

In addition to a characteristic pattern of WMHs, the spectrum of MR abnormalities in CADASIL patients also comprises lacunar infarcts, subcortical lacunar lesions, and microbleeds which were not found in any of our MS patients.

A potential limitation of our study may be that we did not exclude CADASIL in our MS cases by routine screening for *NOTCH3* mutations because of the elaborate and costly nature of the procedure. However, by using the most restricted POSER criteria, namely the laboratory-supported definite MS, we reduced the chance of misclassifying MS patients<sup>99</sup>. In any case, if we would have erroneously misclassified a CADASIL patient as a MS patient, this would have decreased the differences we found between the two patient groups.

In this study, our goal was to assess whether the presence or absence of the radiological hallmarks of CADASIL helped differentiating young CADASIL and MS patients. In other studies MR criteria suggestive of MS have been defined. These MR criteria for MS help further strengthening the diagnostic confidence of differentiating CADASIL from MS. MS frequently involves the spinal cord, while spinal cord lesions are virtually absent in CADASIL<sup>43,44</sup>. WMHs in the subcortical U fibers suggest MS, whereas these fibers are spared in CADASIL<sup>40,101</sup>. The periventricular lesions in MS are frequently ovoid and orientated perpendicular to the lateral ventricles which has not been observed in CADASIL<sup>102</sup>. Gadolinium enhancement of the WMHs frequently occurs in MS, and has not been described in CADASIL patients<sup>41,103</sup>.

CADASIL can be differentiated radiologically from MS already at the young age, primarily on the basis of WMHs in the anterior temporal lobe and the external and internal capsule.

Chapter 6