Magnetic resonance imaging characteristics of CADASIL

Boom, Rivka van den

CADASIL: MR imaging findings at different ages, 3rd-6th decade

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CADASIL: MR imaging findings at different ages, 3rd-6th decade

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Abstract

Purpose was to depict various brain lesions that have been described in patients who have cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) with prospective standardized magnetic resonance (MR) imaging in patients of different age groups.

Forty patients with CADASIL in different age groups (20–30 years, n=5; 31–40 years, n=4; 41–50 years, n=16; 51–60 years, n=15) underwent axial MR imaging with T1-weighted dual fast spin-echo, fluid-attenuated inversion-recovery, and T2*-weighted gradient-echo sequences. Images were analyzed by one neuroradiologist for the presence of areas of hyperintensity, lacunar infarcts, microbleeds, and subcortical lacunar lesions (SLLs) in different anatomic locations. Descriptive statistics were obtained for the presence of MR imaging abnormalities in various brain areas and for distribution according to age.

The mean age of the 40 mutation carriers (21 women, 19 men) was 45 years ± 10 (SD). In patients with CADASIL who were 20–30 years old, characteristic hyperintense lesions in the anterior temporal lobe (100% [five of five]) and SLLs (20% [one of five]) were the only abnormalities seen on MR images. In patients who were 30–40 years old, lacunar infarcts were found in 75% (three of four) of cases. More areas of hyperintensity were noted, and they frequently involved the external capsule, basal ganglia, and brainstem. In patients 41–50 years old, microbleeds were observed in 19% (three of 16). In patients older than 50 years, areas of hyperintensity (100% [15 of 15]), SLLs (73% [11 of 15]), lacunar infarcts (93% [14 of 15]), and microbleeds (47% [seven of 15]) were frequently observed.

The four types of brain lesions that are observed in patients with CADASIL were seen in patients of different age groups.

Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited systemic disease of the small artery caused by mutations in the *NOTCH3* gene on chromosome 19[19]. Histopathological studies of the small and medium-sized leptomeningeal arteries and the long perforating arteries of the brain revealed luminal narrowing or even obliteration caused by deposition of electron-dense granular material close to the membrane of the vascular smooth muscle cells, as well as loss of vascular smooth muscle cells[7]. Clinical manifestations of the disease include ischemic stroke, dementia, migraine with aura, and mood disturbances[75]. The first clinical manifestations of the disease often start in patients during the 3rd decade, and death often occurs in patients during the 6th decade[75]. Main magnetic resonance (MR) imaging findings in patients with CADASIL are diffuse areas of hyperintensity of white matter that occur predominantly in the subcortical areas and lacunar infarcts that are present in the semiovale centre, the thalamus, the basal ganglia, and the pons[39-41]. Recent MR imaging study findings demonstrated microbleeds and subcortical lacunar lesions (SLLs) as additional radiologic features of CADASIL[76-78].

The definite diagnosis of CADASIL is established with detection of *NOTCH3* mutations, and detection of these mutations is a laborious process that is performed at a limited number of specialized centres. Presently, *NOTCH3* mutation analysis is considered only in patients who have unexplained neurologic symptoms, such as ischemic episodes, cognitive deficits, and a positive family history of these symptoms, and who have suggestive MR imaging abnormalities. The radiologic findings of patients with advanced stages of the disease are well documented. On the basis of these descriptions, radiologists can adequately help in the identification of patients with an indication for further molecular or pathologic testing for CADASIL[39-43,67]. However, the radiologic appearances during earlier stages of the disease have not been described in detail, and this lack of information may lead to inadequate guidance of patients through the diagnostic work-up.

To our knowledge, findings of the only published study about the development of cerebral changes over time in patients with CADASIL were reported by Chabriat et al[39]. In that study, the development of areas of hyperintensity and of lacunar infarcts was studied in the periventricular and subcortical white matter, the basal ganglia, and the infratentorial areas. However, after publication of that study, other radiologic hallmarks of CADASIL, such as SLLs, microbleeds, and areas of hyperintensity in the anterior temporal lobe and in the external capsule, were detected[67,76-78]. The temporal evolution of these more recently described radiologic phenomena of CADASIL remains to be

elucidated. Thus, the purpose of our study was to depict various brain lesions that have been described in patients who have CADASIL with prospective performance of standardized MR imaging in patients of different age groups.

Materials and methods

Subjects

Members of 15 unrelated Dutch families who had CADASIL were asked to participate in a study about the clinical, radiologic, and genetic aspects of CADASIL in patients from the Netherlands. In each family, at least one member had a confirmed *NOTCH3* mutation. These patients were referred to Leiden University Medical Centre from various medical centres; this institution serves as a national CADASIL referral centre. The total number of participants was 63 and included symptomatic, as well as asymptomatic, family members. Participants were considered symptomatic when they had a history of neurologic deficits or cognitive decline. The diagnosis of CADASIL was confirmed after the MR imaging examination with identification of pathogenic mutations of the *NOTCH3* gene, as previously described[22].

The families included in this study were all of the families seen between August 1999 and July 2000. To ensure informed consent, only cognitively capable subjects were included in this study. The institutional medical ethics committee approved the study protocol. Since one individual of the 63 participants did not consent to undergo MR imaging, the final number of subjects was 62; 40 of these subjects had a mutation in the *NOTCH3* gene and 22 did not.

MR imaging

All MR imaging examinations were performed with a 1.5-T MR system (Philips Medical systems, Best, the Netherlands). Participants underwent MR imaging with a standardized protocol that included the following: conventional T1-weighted spin-echo (repetition time msec/echo time msec, 600/20; section thickness, 6.0 mm; intersection gap, 0.6 mm; matrix, 256 x 205; field of view, 220 x 165 mm), dual T2-weighted fast spin-echo (3000/27, 120; section thickness, 3.0 mm; intersection gap, 0 mm; matrix, 256 x 205; field of view, 220 x 220 mm), and fast fluid-attenuated inversion-recovery (FLAIR) (repetition time msec/echo time msec/inversion time msec, 8000/100/2000; section thickness, 3.0 mm; intersection gap, 0 mm; matrix, 256 x 192; field of view, 220 x 176 mm) sequences. In addition, a T2*-weighted gradient echo planar (2598/48; section thickness, 6.0 mm; intersection gap, 0.6 mm; matrix, 256 x 192; field of view, 220 x 198 mm; echo-planar imaging factor, 25) sequence was

performed to detect haemosiderin deposits. All images were obtained in the axial plane parallel to the inferior border of the genu and splenium of the corpus callosum.

Areas of hyperintensity were defined as areas of brain parenchyma with increased signal intensity on intermediate, T2-weighted, and FLAIR MR images, and they were rated from hard copies of axial dual T2-weighted fast spin-echo MR images with the semiquantitative visual scoring system described by Scheltens et al[59]. In this scale, the brain is anatomically divided into deep white matter, basal ganglia, and infratentorial regions. For each region, a score of 0–6 is assigned according to the following scale: score 0, absent; score 1, up to five areas of white matter hyperintensity of less than 3 mm in diameter; score 2, six or more areas of white matter hyperintensity of less than 3 mm in diameter; score 3, as many as five areas of white matter hyperintensity of 4–10 mm in diameter; score 4, six or more areas of white matter hyperintensity of 4–10 mm in diameter; score 5, one or more areas of white matter hyperintensity of more than 10 mm in diameter; and score 6, confluent areas of white matter hyperintensity. In addition, scores were assigned to the frontal and occipital periventricular "caps" and periventricular "bands" as follows: score 0, absent; score 1, as much as 5 mm in diameter; and score 2, more than 5 mm in diameter. Because the Scheltens scoring system does not fully reflect the characteristic lesion distribution in patients who have CADASIL, three anatomic locations were added to the Scheltens score: external and internal capsule and the temporal region. The external and internal capsules were assigned separate scores for the presence of areas of subcortical hyperintensity, and the temporal region was assigned a separate score for the presence of areas of periventricular hyperintensity. In our experience, areas of hyperintensity in young patients who have CADASIL often are located in the anterior temporal lobe; for this reason, we assigned separate scores for the presence of areas of hyperintensity in the anterior temporal lobe and the posterior temporal lobe. We defined the border between the anterior temporal lobe and the posterior temporal lobe as the posterior margin of the amygdala[43]. To obtain an overall supratentorial lesion load score, the periventricular score was added to the Scheltens subcortical score. To calculate the prevalence of areas of hyperintensity, a Scheltens score of 1 or higher was considered to be positive for areas of hyperintensity, and a score of 0 implied absence of areas of hyperintensity.

Lacunar infarcts were defined as parenchymal defects that did not extend to the cortical grey matter, with a signal intensity similar to that of cerebrospinal fluid with all pulse sequences, irrespective of size. There are three locations where lacunar infarcts can be difficult to distinguish from normal Virchow-Robin spaces: the basal ganglia, the subinsular region, and the semiovale

centre. To differentiate a lacunar infarct from a Virchow-Robin space, we excluded lesions in the following areas because they were most likely to represent a Virchow-Robin space: (a) basal ganglia: lesions that were isointense to cerebrospinal fluid with all pulse sequences and were located in the lower one-third of the corpus striatum[79,80]; (b) subinsular region: areas with a featherlike configuration that were isointense to cerebrospinal fluid on T1- and T2-weighted MR images but did not have high signal intensity on FLAIR images[73]; (c) semiovale centre: all lesions with a transverse diameter of 2 mm or smaller or with a tubular appearance following the course of perforating arteries[81].

Microbleeds were defined as focal areas of signal intensity loss on T2-weighted fast spin-echo MR images that increased in size on the T2*-weighted gradient-echo images ("blooming effect")[76]. In this way, microbleeds were differentiated from areas of signal loss that were based on vascular flow voids. Areas of symmetric hypointensity of the globus pallidus that were likely to represent calcification or nonhemorrhagic iron deposits were excluded.

SLLs were defined as linearly arranged groups of rounded circumscribed lesions that were just below the cortex at the grey matter–white matter junction and had a signal intensity that was identical to that of cerebrospinal fluid with all pulse sequences[78].

One experienced neuroradiologist (MAvB) who was blinded to the diagnosis of CADASIL assessed the presence of areas of hyperintensity, lacunar infarcts, microbleeds, and SLLs in all 62 participants. For lacunar infarcts and microbleeds, size and number were assessed in the following brain areas: supratentorial region (frontal, temporal, occipital, and parietal lobes and internal and external capsules), infratentorial region (cerebellum, pons, medulla oblongata, and mesencephalon), thalamus, and basal ganglia (globus pallidus, caudate nucleus, and putamen). The presence of SLLs was assessed in each patient who had CADASIL.

Statistical analysis

Descriptive statistics were obtained in regard to the presence of MR imaging abnormalities in various areas of the brain according to age (percentage of patients affected per anatomic structure per decade). Differences in areas of hyperintensity, lacunar infarcts, and microbleeds between male and female patients who had CADASIL were investigated with the Student t-test for unpaired data. Differences in SLLs were tested by using the X^2 test. A difference with $P<0.05$ was considered significant. A statistical software package (SPSS-10; SPSS, Chicago, Ill) was used for data analysis.

Results

Subjects

One individual did not consent to undergo MR imaging. Of the 62 family members who had CADASIL, 40 individuals had a mutation in the *NOTCH3* gene and 22 did not. The mean age of the 40 mutation carriers who were included in our study population was 45 years ± 10 (SD) (range, 21–59 years); 21 women (mean age, 45 years ± 11) and 19 men (mean age, 46 years ± 10) were included. The age and sex distribution of the 40 mutation carriers are listed in table 1. Thirty-two of the 40 *NOTCH3* mutation carriers had a mutation in exon 4; the remaining eight patients had mutations in exon 19, 20, 8, or 11. Thirty-two mutation carriers were clinically symptomatic. The symptoms varied in severity, ranging from one transient ischemic attack to multiple strokes and cognitive decline.

Table 1 Baseline characteristics of NOTCH3 mutation carriers according to age group

Characteristic	20-30 years	31-40 years	41-50 years	51-60 years
No. of patients	5	4	16	15
Sex				
M	2	2	7	7
F	3	2	9	8
Clinical manifestation				
Symptomatic	0	3	14	15
Asymptomatic	5	1	2	0

MR imaging

Figure 1 shows the prevalence of areas of hyperintensity, SLLs, lacunar infarcts, and microbleeds among patients of different age groups. Areas of hyperintensity were observed in all mutation carriers. The load of areas of hyperintensity as quantified with the Scheltens score did not differ significantly (P=0.5) between men (mean score, 52) and women (mean score, 48). Thirty-two (80%) of 40 mutation carriers had lacunar infarcts, with a mean of 19 (range, 1–60) lacunar infarcts per patient. This group of mutation carriers with lacunar infarcts had a mean age of 49 years ± 6 (age range, 38–59 years). Men had significantly (P=0.01) more lacunar infarcts (n=22) than did women (n=9). Microbleeds were found in ten (25%) mutation carriers, with a mean age of 53 years ± 5 (age range, 43–58 years). Per patient, a mean of nine microbleeds (range, 1–35) was found. The prevalence of microbleeds did not differ significantly (P=0.3) between men and women. Twenty-two (55%)

mutation carriers with a mean age of 49 years ± 8 (age range, 25–59 years) had SLLs. SLLs were significantly (P=0.02) more prevalent in men (n=14) than they were in women (n=8).

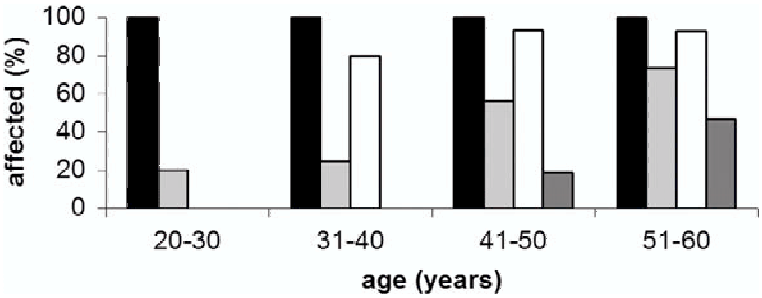

Figure 1 Graph shows prevalence of areas of hyperintensity (black bars), SLLs (light grey bars), lacunar infarcts (white bars), and microbleeds (dark grey bars) in different age groups. Areas of hyperintensity were present in all mutation carriers. SLLs were found in patients in the 3rd decade and older; lacunar infarcts, in those in the 4th decade and older; and microbleeds, in those in the 5th decade and older.

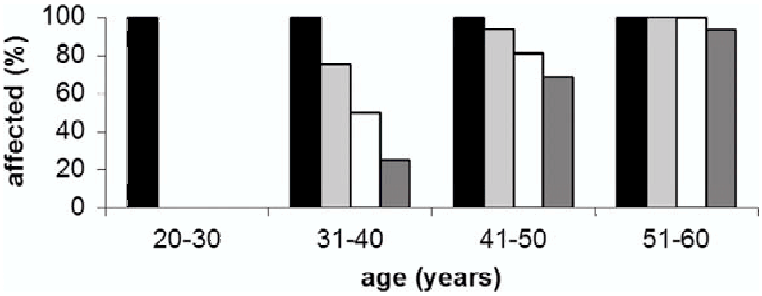

Figure 2 Graph shows prevalence of areas of hyperintensity per location in relation to age. In patients in the 3rd decade, only supratentorial areas of hyperintensity (black bars) were present. With increasing age, areas of hyperintensity were found in other locations too. In patients in the 6th decade, almost all mutation carriers had areas of hyperintensity in every region. Areas of hyperintensity were observed in the following areas: thalamus (white bars), infratentorial region (light grey bars), and basal ganglia (dark grey bars).

Figure 2 shows the prevalence of areas of hyperintensity in different age groups classified according to the supratentorial white matter, the infratentorial structures, the basal ganglia, and the thalamus. In patients in the 3rd decade, only areas of hyperintensity in the supratentorial white matter were present (figure 3). Areas of hyperintensity in the infratentorial structures, the basal ganglia, and the thalamus were present in patients in the 4th decade. In the 6th decade, all mutation carriers had areas of hyperintensity in each compartment. To further characterize the distribution of areas of hyperintensity

within the supratentorial white matter at different times, we subcategorized this compartment into several anatomic regions and assessed the presence of areas of hyperintensity in the different age groups (figure 4). In all young mutation carriers, subtle areas of hyperintensity in the anterior temporal lobe were found (figure 3). Although the occipital lobe was less affected in patients younger than 40 years as compared with other lobes, all lobes were equally affected in patients older than 40 years. Areas of hyperintensity in the external capsule were present in patients older than 30 years; areas of hyperintensity in the internal capsule were seen in patients older than 40 years (figures 5, 6). Frontal periventricular areas of hyperintensity and periventricular bands were seen in four mutation carriers; temporal periventricular areas of hyperintensity, in two mutation carriers; and occipital periventricular areas of hyperintensity, in one mutation carrier younger than 30 years. The total periventricular Scheltens score in this group varied between 0 and 4. In patients older than 30 years, all mutation carriers had periventricular areas of hyperintensity in every region. With the exception of one mutation carrier who had a score of 3, all other patients had a total periventricular Scheltens score that varied between 6 and 8, the maximal score for periventricular areas of hyperintensity.

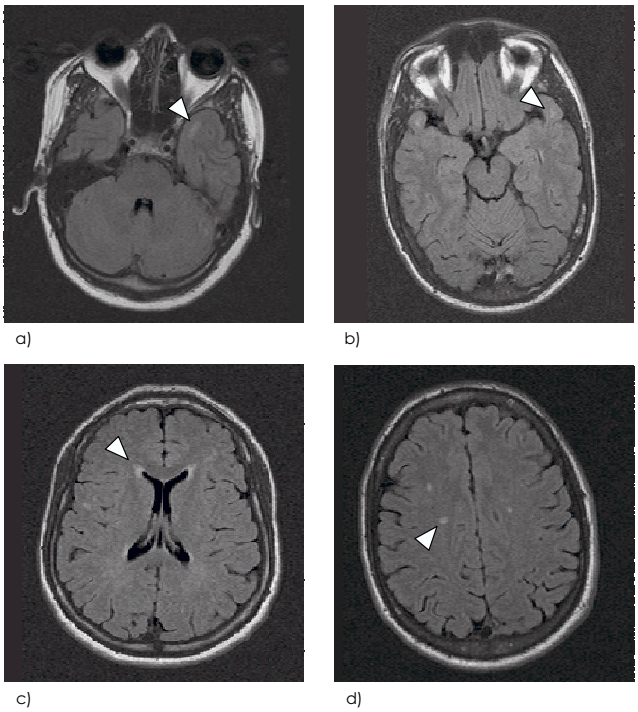

Figure 3 Axial FLAIR MR images in NOTCH3 mutation carriers who were 20-30 years old (a-d). Image shows areas of hyperintensity (arrowhead in a) in the anterior temporal lobe. Image shows SLLs (arrowhead in b). Image shows small ventricular caps (arrowhead in c). Image shows small areas of hyperintensity in the semiovale centre (arrowhead in d).

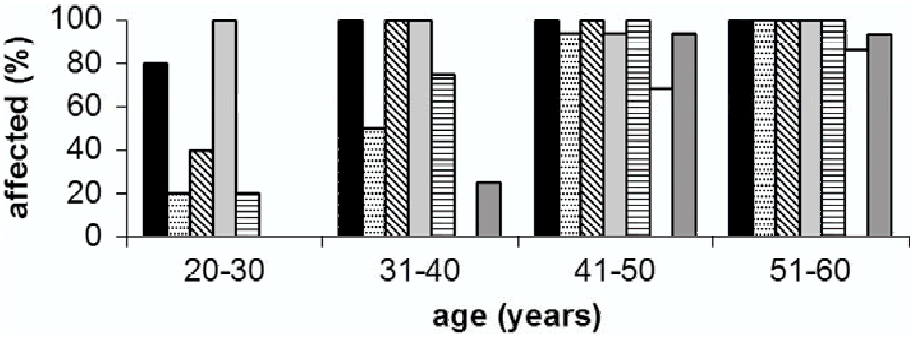

Figure 4 Graph shows supratentorial areas of hyperintensity distributed among the different regions according to age. In the 3rd decade in all mutation carriers, areas of hyperintensity were observed in the anterior temporal lobe. Areas of hyperintensity were found in the external capsule in patients in the 4th decade and older and in the internal capsule in patients in the 5th decade and older. Areas of hyperintensity were observed in the following regions: frontal lobe (black bars), occipital lobe (dotted bars), parietal lobe (diagonally striped bars), temporal anterior lobe (light grey bars), temporal posterior lobe (horizontally striped bars), internal capsule (white bars), and external capsule (dark grey bars).

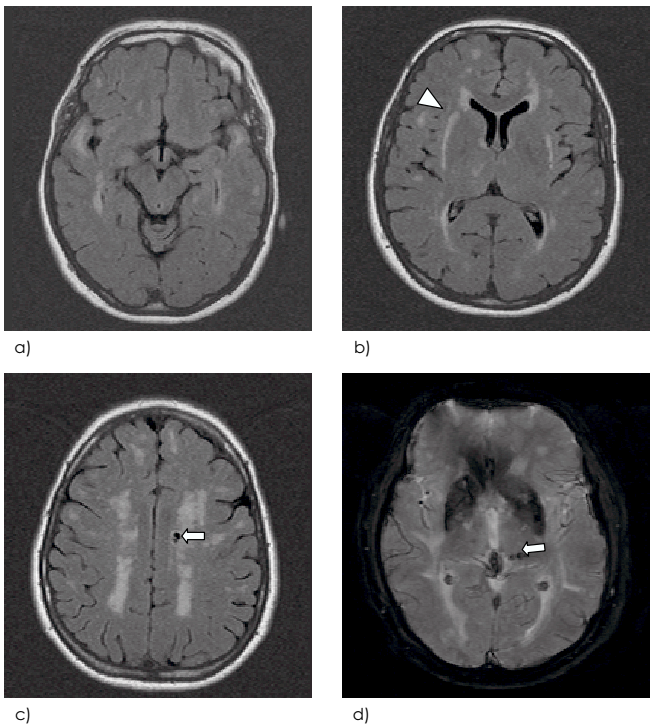

Figure 5 Axial FLAIR MR images (a-c). T2-weighted gradient-echo MR image (d). Images obtained in NOTCH3 mutation carriers who were 41-50 years old show confluent areas of hyperintensity in all lobes (a-c). Involvement of the external capsule (arrowhead) is an important feature at this age. Lacunar infarcts (arrow in c) and microbleeds (arrow in d) are present.*

Of the total 606 lacunar infarcts, 249 were located in the basal ganglia; lacunar infarcts were also found in the frontal lobe (n=125), the parietal lobe (n=129), the temporal lobe (n=44), the pons (n=27), the thalamus (n=22), the cerebellum (n=5), the occipital lobe (n=4), and the mesencephalon (n=1). Only 10 (1.7%) lacunar infarcts were larger than 10 mm in diameter. Figure 7 shows the prevalence of lacunar infarcts per location in the different age groups. The supratentorial lacunar infarcts were seen in patients in the 4th decade, and their prevalence was greater in those during the 5th decade (figures 5, 6, 8). Lacunar infarcts in the basal ganglia were present in patients in the 4th decade. In patients in the 5th decade, their prevalence was 81%, and this percentage was the same in patients during the 6th decade. In the 6th decade, *NOTCH3* mutation carriers had lacunar infarcts in the infratentorial region (53%) and in the thalamus (47%).

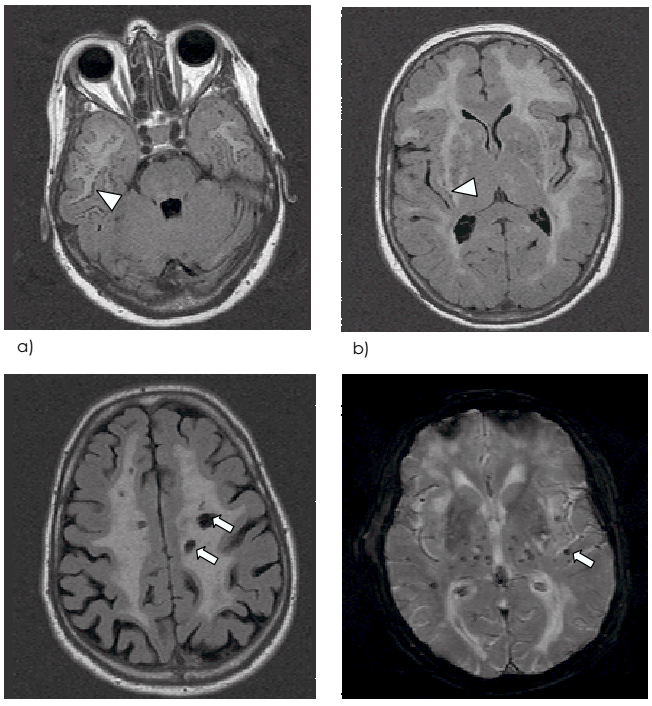

Figure 6 Axial FLAIR MR images(a-c). T2-weighted gradient-echo MR image(d). Images obtained in NOTCH3 mutation carriers who were 51-60 years old show complete penetrance of CADASIL: confluent areas of hyperintensity (a-c), lacunar infarcts (arrows in c), SLLs (arrowheads), and microbleeds (arrow in d).*

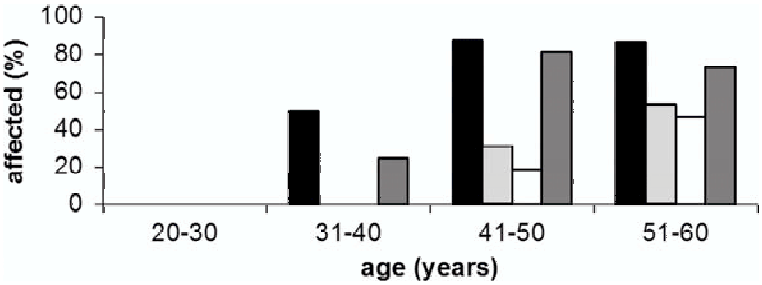

Figure 7 Graph shows prevalence of lacunar infarcts per location in relation to age. In patients in the 4th decade, lacunar infarcts were present in the supratentorial region (black bars) and in the basal ganglia (dark grey bars). Lacunar lesions in the infratentorial region (light grey bars) and in the thalamus (white bars) were present in patients older than 40 years.

The distribution of the total 85 microbleeds was as follows: thalamus (n=53), occipital lobe (n=11), temporal lobe (n=5), cerebellum (n=5), brainstem (n=4), parietal lobe (n=4), basal ganglia (n=2), and frontal lobe (n=1). Seventy-eight (92%) microbleeds were smaller than 5 mm in diameter; the largest was 10 mm in diameter (figures 5, 6). The prevalence of microbleeds per location in the different age groups is illustrated in figure 9.

Discussion

The spectrum of MR imaging abnormalities in patients who have CADASIL has been described in several studies[39-43,77,78]. These abnormalities include areas of hyperintensity, lacunar infarcts, a characteristic pattern of SLLs, and microbleeds. To the best of our knowledge, this study is the first to determine the presence of these lesions, on the basis of radiologic appearances in patients with CADASIL during the 3rd, 4th, 5th, and 6th decades.

As early as the 3rd decade, cerebral abnormalities can be found in patients who have CADASIL. In this study, supratentorial areas of hyperintensity were observed in all patients, and SLLs were observed in one patient. A notable site of predilection of the areas of hyperintensity is the anterior temporal lobe. These areas of hyperintensity are found in all patients of this age group, invariably as a highly characteristic pattern of bilateral hyperintense areas located directly below the cortical ribbon. Although this type of abnormality has been described by others as a characteristic finding in patients who have CADASIL, the early involvement of the anterior temporal lobe has not been reported before, to our knowledge[67]. A pattern of multiple, although often few, small patches with high signal intensity was observed in other locations. Periventricular white matter areas of hyperintensity are frequently seen as smooth caps around the frontal horns and seldom are seen around

the posterior and temporal horn of the lateral ventricles. In young patients, SLLs were another characteristic observation, and SLLs always were observed in conjunction with the observation of areas of hyperintensity in the anterior temporal lobe. SLLs are a recently described abnormality that is considered to be specific for CADASIL[92]. The radiologic phenomenon of SLLs is based on the presence of dilated perivascular spaces of perforating arteries at the level of the grey matter–white matter junction and spongiosis in the surrounding parenchyma. Detection of areas of hyperintensity with or without SLLs in the anterior temporal lobes in young patients is highly characteristic of findings in young patients with CADASIL, and detection of these areas of hyperintensity suggests the diagnosis.

In the 4th decade, in addition to areas of hyperintensity and SLLs, lacunar infarcts were seen in patients who have CADASIL. These lacunar infarcts are found in 75% of patients of this age group, and they occur in the supratentorial white matter and in the basal ganglia. In the supratentorial white matter, areas of hyperintensity in the external capsule are a new finding in this age group, and this finding can be observed in 25% of patients. The prevalence of subcortical areas of hyperintensity increases in all lobes, and larger periventricular areas of hyperintensity are present. Subcortical and periventricular areas of hyperintensity may become confluent. The areas of hyperintensity in the anterior temporal lobe increase in size and expand posteriorly in the temporal lobe. Apart from the supratentorial white matter, areas of hyperintensity are now also observed in the basal ganglia, the thalamus, and the brainstem. Although the number of patients in whom SLLs are observed does not increase, the number of SLLs per patient is higher than it is in the preceding age group, and the distribution of SLLs follows the expanding white matter areas of hyperintensity of the anterior temporal lobes.

In patients in the 5th decade, microbleeds may be observed in addition to areas of hyperintensity, SLLs, and lacunar infarcts. Microbleeds are found in 19% of patients in this age group, and they can be observed in the thalamus, the brainstem, and the supratentorial white matter. The number of patients in whom areas of hyperintensity are observed further increases, although there are still patients in whom areas of hyperintensity are not observed in the infratentorial white matter, in the basal ganglia, or in the thalamus. The number and size of areas of hyperintensity further increase, giving rise to large confluent areas of high signal in subcortical and periventricular white matter. Areas of hyperintensity can also involve the internal capsule. The prevalence of lacunar infarcts (94%) and SLLs (56%) increases. Now lacunar infarcts also are present in the brainstem and the thalamus.

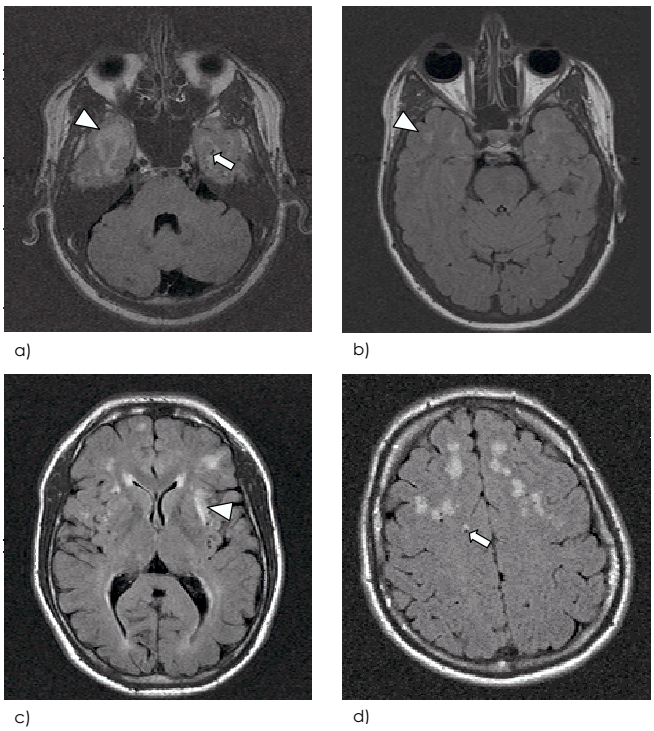

Figure 8 Axial FLAIR MR images obtained in NOTCH3 mutation carriers who were 31-40 years old. At this age, areas of hyperintensity (arrowhead in a and b) and SLLs (arrow in a) expand from the anterior temporal lobe posteriorly and affect the whole temporal lobe. Areas of hyperintensity in the semiovale centre become larger. Areas of hyperintensity in the external capsule (arrowhead in c) and lacunar infarcts (arrow in d) are present.

In patients in the 6th decade, no new types of lesions are seen, and areas of hyperintensity, SLLs, lacunar infarcts, and microbleeds are observed in most patients. Areas of hyperintensity are always found in all lobes, in the brainstem, in the basal ganglia, and in the thalamus. In almost all cases, areas of hyperintensity are also found in the internal and external capsule. During this stage, most of the supratentorial white matter may show a symmetric pattern of large homogeneous areas of increased signal intensity involving the subcortical and periventricular white matter. Lacunar infarcts are found in more than 90% of cases. SLLs are found in 73% of cases; microbleeds, in 47%. SLLs may now be observed in the temporal lobe, in the subinsular white matter, and in the operculum of the frontal lobe.

In patients older than 30 years, CADASIL shares several radiologic characteristics with other diseases accompanied by small vessel disease, which implies that differentiating CADASIL from these disorders based on findings of radiologic examinations may be difficult. Nonspecific areas of hyperintensity in the periventricular, the frontal, the parietal, and the occipital regions are seen

in a number of other small vessel diseases[82]. Brainstem abnormalities located predominantly at the rostrocaudal centre of the pons are frequently observed in patients who have CADASIL, but they can also be found in patients who have atherosclerosis[83]. The occurrence of lacunar infarcts and microbleeds is also considered to be characteristic of cerebral small vessel disease in general and is not characteristic of only CADASIL[55,84]. Still, the distribution of the areas of hyperintensity and the presence of SLLs seem to specifically suggest the diagnosis of CADASIL. By using image post processing software that is based on statistical parametric mapping, Auer et al compared patterns of areas of hyperintensity in a group of patients who had CADASIL and a group of patients who had Binswanger's disease[67]. In that study, it was suggested that the presence of white matter areas of hyperintensity in the anterior temporal lobe was characteristic of patients who had CADASIL. The image processing technique used in that study only permitted detection of differences between groups and did not help in determination of the diagnosis in patients. In our study, the characteristic areas of hyperintensity in the anterior temporal lobe were present in 39 of 40 patients who had CADASIL, and this result demonstrates that the prevalence of this finding in patients who have CADASIL is high, which makes it a useful radiologic hallmark of the disease. The presence of areas of hyperintensity in the external capsule also has been described to be characteristic of CADASIL[43]. Because of its high prevalence (94%) among patients with CADASIL after the age of 40, this is another sign that is helpful in the suggestion of the diagnosis later during the course of the disease. Finally, the prevalence of SLLs increases considerably in patients older than 40 years, and therefore, this lesion is helpful for detection of the disease in patients with increasing age.

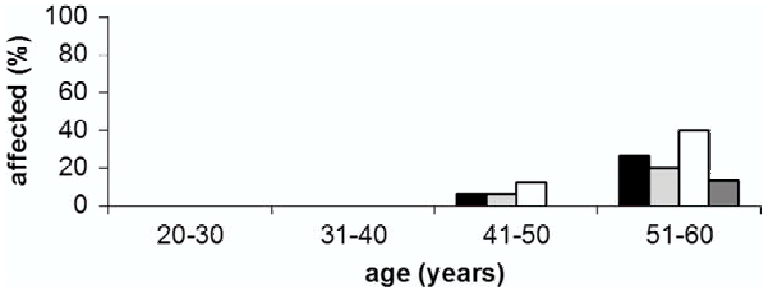

Figure 9 Graph shows prevalence of microbleeds per location in relation to age. Microbleeds were present in patients older than 40 years, predominantly in the thalamus (white bars). Graph also shows data for those observed in the following areas: supratentorial region (black bars), infratentorial region (light grey bars), and basal ganglia (dark grey bars).

In our study, men were more frequently affected by lacunar infarcts and SLLs than were women. For this observation, there is no simple explanation. A difference in age at death between men and women who have CADASIL has been found[19]. Death occurs at a significantly younger age in men, and although this difference may reflect the generally observed difference in life expectancy, it may also be caused by differences in the disease dynamics in men and women.

In summary, in patients who have CADASIL, imaging abnormalities are found in the brain earlier than expected clinically. In young patients who have CADASIL, cerebral abnormalities are highly characteristic, although limited. The areas of hyperintensity in the anterior temporal lobe and the SLLs that are observed in these young patients continue to help in the recognition of the underlying condition later in life.