Magnetic resonance imaging characteristics of CADASIL

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Summary and conclusions

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Magnetic resonance (MR) imaging plays an important role in the diagnostic work-up of CADASIL patients. This thesis describes the typical appearance of MR abnormalities in CADASIL patients, the natural history of these abnormalities, and the differences of these lesions as compared to the lesions that occur in multiple sclerosis (MS). Also included are the results of a study on the influence of apolipoprotein E (apoE) genotype and a study of cerebral blood flow on the development of MR abnormalities.

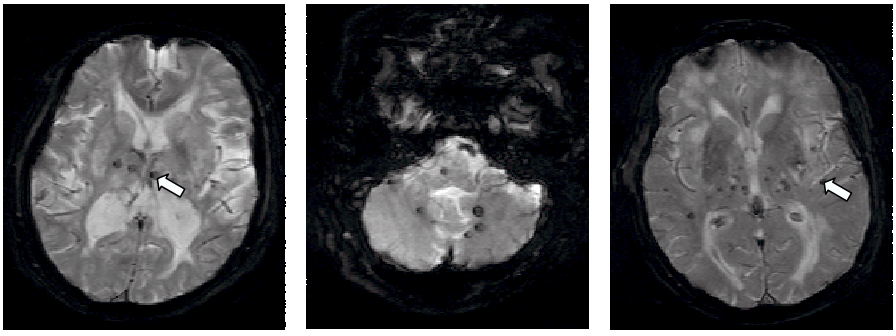
In chapter 1 a short introduction is given on the aetiology and clinical appearance of CADASIL, the initial radiological descriptions of cerebral lesions, and the role of imaging in the diagnostic work-up of these patients. Furthermore the goal and outline of this thesis are portrayed.

In chapter 2 we assessed whether microbleeds are present in CADASIL and, if so, whether they are associated with other patient characteristics. Several studies have shown that microbleeds are associated with the presence of intracerebral haemorrhage. Although there are some descriptions on the occurrence of intracerebral haemorrhage in patients with CADASIL, the prevalence of haemorrhages in CADASIL patients was unknown at the start of this study. By using a T2* gradient-echo technique, detection of haemosiderin deposits reflecting remnants of intracerebral microbleeds is possible. In this study we found that 31% of symptomatic CADASIL patients had microbleeds on MR imaging, predominantly in the thalamus (figure 1). This suggests that CADASIL patients might be at risk for developing intracerebral haemorrhage.

In chapter 3 we describe a new radiological finding in CADASIL patients, the so called subcortical lacunar lesions (SLLs). SLLs are linearly arranged groups of rounded, circumscribed lesions just below the cortex, at the grey white matter junction with a signal intensity that is identical to that of CSF on all pulse sequences. These lesions are best seen on thin sections (3mm) fluid-attenuated inversion-recovery (FLAIR) images (figure 2a,b). SLLs were found in 59% of CADASIL patients, and when present, SLLs invariably occurred in the anterior temporal lobe, always in combination with white matter hyperintensities (WMHs). Because none of the control subjects showed SLLs, we believe that SLLs are highly characteristic for CADASIL and detection of SLLs might help in establishing de diagnosis of CADASIL. Histological examination revealed that the lesions are caused by a distention of the perivascular space of perforating arteries (figure 2c).

In chapter 4 we describe the natural history of the various brain lesions that can be observed in CADASIL patients. These lesions include not only WMHs and lacunar infarcts but also the recently reported microbleeds and SLLs. The results of this study showed that these lesions develop in a predictable way

during the course of the disease. Hyperintensities were present in all CADASIL patients, increasing with age and with a predilection for the temporal and frontal lobe (figure 3). In young CADASIL patients (20-30 years), hyperintensities in the anterior temporal lobe, in one patient in combination with SLLs, are the only abnormalities seen on MR imaging. The development of lacunar infarcts starts in the fourth decade. Microbleeds occurred during the fifth and sixth decade. In patients older than 50 years all four abnormalities were frequently observed. Knowledge of these age dependent MR patterns should help to make the diagnosis of CADASIL.



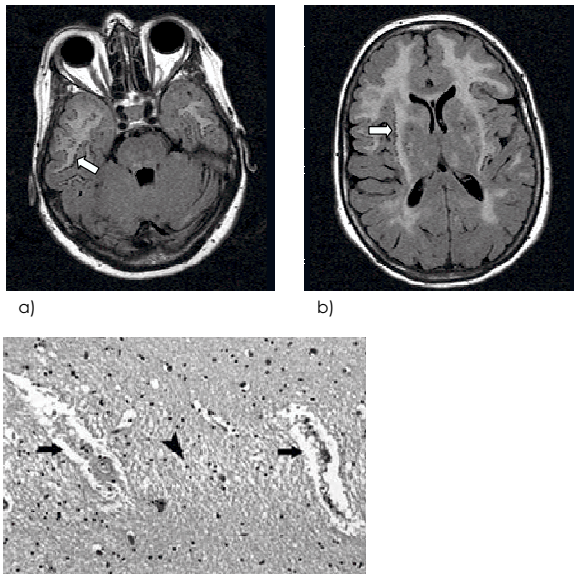
a) b) c)

Figure 1 Axial T2-weighted gradient echo planar images show numerous microbleeds, located in the thalamus, cerebellum as well as deep and subcortical white matter (arrows).*

In chapter 5 we describe the results of a study in which we compared the neuropsychological, clinical, and neuroradiological features of CADASIL patients and controls between 21 and 35 years of age. The main results were that there was no quantifiable physical or cognitive impairment in young CADASIL patients. Disease expression was only confined to migraine and, less frequently, TIA and (minor) stroke. Radiologically, a characteristic MR lesion pattern was present in all CADASIL patients. WMHs, sometimes subtle, were present in the frontal lobes and periventricular frontal caps, but most importantly, first appeared in the anterior temporal lobe (figure 3).

In chapter 6 we compared the radiological appearance of CADASIL to that of multiple sclerosis (MS), a disease with clinical and radiological similarities to CADASIL. CADASIL patients showed significantly more SLLs and hyperintensities in the anterior temporal lobe and the external capsule compared with MS. Although in general practice the prevalence of MS is higher than of CADASIL, the hyperintensities in the anterior temporal lobe especially in combination

with one of the other CADASIL MR hallmarks should lead to the diagnosis of CADASIL. MR imaging permits discriminating between CADASIL and MS, even at a young age, so that misdiagnosis can be avoided.



a) b)

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Figure 2 Axial FLAIR MR images show SLLs affecting the anterior part of the temporal lobe (a) and the subinsular region (b). 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.).

In chapter 7 the influence of apoE genotype on the development of structural brain lesions of CADASIL is studied. The apoE genotype, a well known genetic risk factor for Alzheimer's disease and sporadic cerebral amyloid angiopathy, does not influence the amount of structural cerebral changes as seen on MR imaging in CADASIL patients. Therefore other genetic or non-genetic factors probably underlie the variable natural history of the disease.

Chapter 8 deals with the question whether a decrease in cerebral blood flow or cerebrovascular reactivity is primarily responsible for the development of WMHs and lacunar infarcts. To address this issue, phase contrast MR imaging was used to assess baseline total cerebral blood flow and cerebrovascular reactivity after acetazolamide. The response on acetazolamide was not decreased relative to the baseline total cerebral blood flow. However, the mean baseline total cerebral blood flow was significantly decreased in

patients with CADASIL. These findings suggest that vascular stenosis plays a larger role in the development WMHs and lacunar infarcts in CADASIL patients, than diminished vascular reactivity.

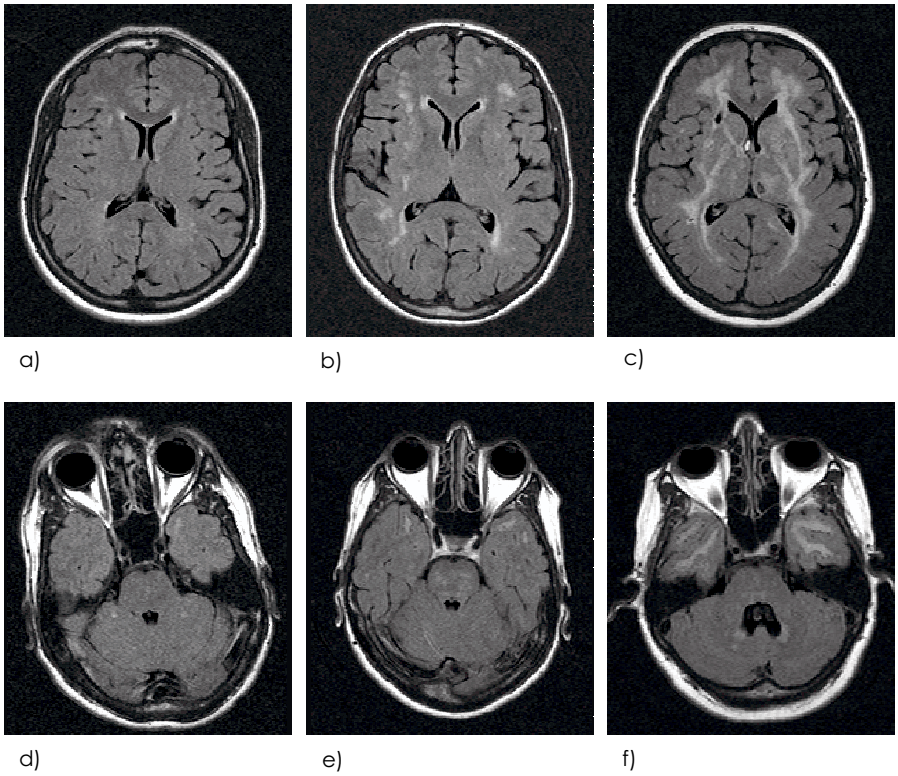

Figure 3 FLAIR MR images of three mutation carriers aged 26, 46 and 53 years. Axial slices through the level of the temporal lobes and basal ganglia showing the development of WMHs in the temporal lobe and external and internal capsule.