Disease progression and high field MRI in CADASIL

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Chapter 9

Summary and conclusion

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Chapter 1 is an introductory chapter to clinical, genetic, histopathological and radiologic aspects of CADASIL. A survey is given of various aspects of disease progression in CADASIL that are incompletely understood, and of some unresolved issues of CADASIL that can be answered with high field MRI. The aims of this thesis are described: to gain a better understanding of disease progression in CADASIL, by using MRI techniques on standard field strengths (1,5 and 3 Tesla) and to increase insight into cerebral changes in CADASIL by using high field MRI (7 Tesla).

In **chapter 2** we prospectively investigated the pattern and rate of MRI abnormality progression in a CADASIL cohort 7 years after baseline, to identify prognostic factors that determine the rate and pattern of this progression. Twenty-five *NOTCH3* mutation carriers and 13 non-mutation carriers from 12 unrelated families were clinically investigated and had standardized MRI examinations on 1,5 Tesla at baseline and after 7 years. Mutation carriers showed a significant increase in lesion load of lacunar infarcts, white matter hyperintensities and number of microbleeds, but no increased loss of brain volume compared to non-mutation carriers. High lesion loads of WMHs, lacunar infarcts and microbleeds at baseline, but not cardiovascular risk factors, were associated with faster progression of these lesions. CADASIL patients with a high MRI lesion load at baseline are at risk for faster progression of MRI abnormalities.

In **chapter 3** we studied to what extent lacunar infarcts, WMHs and microbleeds on MRI contribute to cognitive dysfunction in CADASIL. Neuropsychological tests and MRI examinations were performed in 40 *NOTCH3* mutation carriers and 22 healthy controls. Severity of cognitive dysfunction in mutation carriers was independently associated with MRI infarct lesion load ($P<0.05$). In contrast, WMH lesion load and microbleeds were not associated with cognitive dysfunction after correcting for age. Lacunar infarct lesion load appears to be the most important MRI parameter associated with cognitive dysfunction in CADASIL.

In **chapter 4** we performed a follow-up study on the same research cohort from chapter 3, in order to determine whether there are associations between different radiologic hallmarks in CADASIL and decline in specific cognitive domains. Twenty-five NOTCH3 mutation carriers and 13 controls had standardized neuropsychological testing and MRI examinations at baseline and after a follow-up of 7 years. At follow-up, mutation carriers showed a decline in global cognitive function (CAMCOG, $p < 0.01$) and in the cognitive domains language, memory, and executive function, compared to controls. Increase in lacunar infarcts, micro-

bleeds, and ventricular volume, but not white matter lesions or atrophy, were associated with cognitive decline.

In **chapter 5** we investigated the role of total cerebral blood flow (TCBF) and cerebrovascular reactivity (CVR) in the progression of MRI abnormalities in CADASIL. Basal TCBF was measured in 25 NOTCH3 mutation carriers and 13 controls at baseline. CVR after administration of acetozolamide was measured in 14 NOTCH3 mutation carriers and 9 controls. Increase in white matter hyperintensities (WMHs), lacunar infarcts and microbleeds on MRI was measured 7 years later. Lower CVR at baseline was associated with larger increase of WMHs but not with larger increase of lacunar infarcts or microbleeds. TCBF at baseline was not associated with increase of MRI abnormalities. Decreased CVR is a potential predictor of disease progression as indicated by increasing WMHs in CADASIL. As CADASIL is good model for sporadic small vessel disease, longitudinal studies in selected populations at risk are warranted to investigate the role of CVR in the pathophysiology of sporadic small vessel disease.

In **chapter 6** we studied a CADASIL patient with a homozygous NOTCH3 mutation, using standardized neuropsychological and MRI examinations. We compared her clinical phenotype to a brother with a heterozygous mutation and a sister without a mutation. The clinical phenotype of both our homozygous patient and her heterozygous brother was at the more favourable end of the spectrum of CADASIL. This provides evidence that heterozygous and homozygous CADASIL patients are clinically indistinguishable. The fact that a homozygous mutation does not aggravate the clinical phenotype, suggests that the pathogenetic mechanism is most likely based on a toxic effect due to the accumulation of the mutated NOTCH3 protein or on other gain of function effects.

In **chapter 7** we used high-field MR-angiography (MRA) to examine the luminal diameters of lenticulostriate arteries in living CADASIL patients and to investigate whether luminal narrowing is correlated with the number of lacunar infarcts in the basal ganglia. For this purpose, 22 NOTCH3 mutation carriers and 11 healthy controls were examined with 3D-time-of-flight magnetic resonance angiography on a 7-Tesla MRI scanner. We observed that CADASIL patients have normal lengths and luminal diameters of lenticulostriate arteries, and that luminal diameters of lenticulostriate arteries are not associated with lacunar infarct load in the basal ganglia. This suggests that lacunar infarcts in the basal ganglia in CADASIL patients do not result from luminal narrowing of these vessels, but possibly from other haemodynamic disturbances.

In **chapter 8** we used in-vivo and ex-vivo MRI, combined with post-mortem histopathologic analysis, to study diffuse iron deposition in CADASIL. Twenty-five NOTCH3 mutation carriers and 15 healthy controls were examined using high resolution T2*-weighted imaging on a

7 Tesla whole body MRI scanner. Ex-vivo brain specimens of another 3 CADASIL patients were analyzed for iron deposition using ex-vivo MRI as well as histopathological analysis. In-vivo MRI showed that, compared to healthy controls, mutation carriers have decreased signal intensity and increased phase shift in the putamen and caudate nucleus, suggestive of increased diffuse iron accumulation. Ex-vivo MRI and histopathologic analysis confirmed the presence of increased iron deposition in these nuclei. These results suggest that progressive iron deposition plays a role in CADASIL.

CONCLUSIONS AND DISCUSSIONS

Lacunar infarcts, white matter hyperintensities and microbleeds are progressive in patients with CADASIL. Vascular risk factors and the presence of migraine phenotype has no significant effect on disease progression in our studies when specifically looking at rate of progression of MRI abnormalities. However, we did find that patients with a high MRI lesion load at baseline are at risk for faster progression of these abnormalities. With respect to patient care and counselling this means that patients with a high MRI lesion load may require more frequent clinical monitoring and MR imaging follow-up than patients with a low MRI lesion load.

Lacunar infarcts, microbleeds and increased ventricular volume, but not white matter lesions or global atrophy, are associated with cognitive decline in CADASIL. These MRI abnormalities may be the most relevant parameters to monitor disease severity in CADASIL in a clinical setting or research setting. It can be hypothesized that these MRI abnormalities are also more strongly associated with cognitive decline in other types of vascular dementia.

Progression of WMHs in CADASIL is associated with decreased cerebrovascular reactivity but not with basal total cerebral blood flow. Again, it would be interesting to study whether this association is also present in other types of vascular dementia.

Patients with a homozygous *NOTCH3* mutation have a similar clinical phenotype as patients with a heterozygous mutation. This suggests that the pathogenetic mechanism of the NOTCH3 mutation at the protein level is most likely based on a toxic effect due to the accumulation of the mutated NOTCH3 protein or on other gain of function effects.

Luminal diameters of lenticulostriate arteries are normal in CADASIL, and lacunar infarcts in the basal ganglia in CADASIL patients do not result from luminal narrowing of these vessels. This suggests that the mechanism leading to basal ganglia ischemia in CADASIL is not attributable to generalized narrowing of lenticulostriate arteries, but possibly to other haemodynamic disturbances such as cerebrovascular reactivity. With respect to small vessel

disease in general, the hypothesis can be made that generalized narrowing of lenticulostriate arteries is not a prerequisite for development of basal ganglia infarcts.

Increased diffuse iron accumulation in the putamen and caudate nucleus is part of the pathophysiology in CADASIL. Apparently, the process of increased iron accumulation is not exclusive to degenerative or metabolic brain disorders, but can also be caused by a vascular brain disease such as CADASIL. Possibly iron deposition is also increased in other vascular brain diseases, including vascular dementia.