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Disease progression and high field MRI in CADASIL

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Chapter 1

Introduction

INTRODUCTION

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary microangiopathy caused by mutations of the *NOTCH3* gene. The microvascular changes are systemic, but the brunt of the abnormality affects the cerebral vasculature.(1) Clinical hallmarks are recurrent stroke, cognitive decline, migraine with aura (in up to 40% of patients), and mood disorders (in up to 30% of patients).(2) Magnetic resonance (MR) imaging invariably reveals characteristic areas of white matter hyperintensity (WMH) with or without subcortical lacunar lesions,(3) lacunar infarcts, and microbleeds in both symptomatic and asymptomatic adult human mutation carriers.(4;5)

Increasing insight into CADASIL disease progression and its associated factors will help the search for intervention strategies that can modify the disease course. Since CADASIL is sometimes considered a model disease for other more prevalent brain diseases such as vascular dementia and migraine, studying CADASIL may also help to increase insight into those diseases. With respect to vascular dementia, the relatively young age of CADASIL patients make it possible to study the effect of vascular changes to the brain parenchyma, without possible confounding effects of degenerative brain disease.

In this introduction a summary of the clinical, genetic, pathological, and radiological aspects of CADASIL will be given and the aims of this thesis will be described.

CLINICAL PRESENTATION

The most frequent symptoms of CADASIL are migraine with aura, cerebrovascular incidents, cognitive dysfunction and behavioral abnormalities.(2) Clinical presentation as well as age of onset vary widely between patients. Typically, first symptoms appear around the age of 20-45 years, although asymptomatic patients of older age have been described. The mean age of death is 60 years.

Around 30% of CADASIL patients have migraine attacks, of which the majority are with aura. (6) With an average age of onset of 26 years, migraine with aura is often the first symptom of the disease. Migraine aura in CADASIL is frequently atypical or prolonged.

Transient ischaemic attacks and ischaemic strokes appear around the age of 30-45 years. They occur in 60-85% of CADASIL patients. Most patients have recurrent strokes, which lead to progressive motor impairment, urine incontinence and pseudobulbar palsy.

Cognitive deficits have been demonstrated from the age of 35, typically starting with impairment of executive function. Cognitive decline can be gradually progressive or stepwise progressive with recurrent strokes. In more than 80% of the patients a marked global cognitive decline occurs before the age of 60.

Neuropsychiatric symptoms consist mainly of depression and apathy.(7)

GENETICS OF CADASIL

CADASIL is an autosomal dominant disease, caused by mutations of the *NOTCH3* gene.(8) More than 150 mutations have been reported in at least 500 pedigrees. The gene encodes the NOTCH3 protein, a transmembrane receptor that is predominantly expressed in vascular smooth muscle cells and pericytes. The extracellular domain of the protein consists of 34 epidermal growth factor-like repeats (EGFR), each containing six cysteine residues. These cysteine residues form disulfide bonds. Ligands on juxtaposed cells bind to the extracellular domain, triggering a signaling cascade with translocation of the intracellular domain to the nucleus, where it functions as a regulator of transcription. CADASIL mutations all lead to an uneven number of cysteine residues in one of the 34 EGFR domains.(9) The exact mechanism whereby the mutated NOTCH3 protein leads to the vasculopathy of CADASIL remains to be determined. One of the current hypotheses is that there is a toxic gain of function, where the unpaired cysteine residue leads to increased multimerization of the mutated protein. This causes accumulation of the protein on the surface of vascular smooth muscle cells, which may be either directly or indirectly detrimental to vascular smooth muscle cell homeostasis and function.(10)

HISTOPATHOLOGIC FINDINGS

Post mortem examination of the brain typically shows multiple lacunar infarcts throughout the subcortical white matter as well as in the basal ganglia and thalamus, and diffuse myelin pallor and rarefaction of the white matter predominating in periventricular areas and centrum semiovale.(1) Histopathological findings in CADASIL consist of degeneration of cerebral vascular smooth muscle cells with adjacent deposits of granular osmiophilic material (GOM) and fibrous thickening of the arterial walls. These changes can be demonstrated in arteries of systemic organs as well, such as the liver, spleen, kidney and skin. However the most severely affected vessels are the leptomeningeal arterioles and the lenticulostriate arterioles of the brain.(11) It is believed that the pathologic changes in these vessels lead to a reduction in blood flow and an impairment in ability to regulate blood flow (cerebrovascular reactivity).

In the clinical setting, skin biopsy samples can be used to confirm the diagnosis of CADASIL. Electron-microscopy shows GOM within the vascular media close to smooth muscle cells, whereas immunostaining of skin samples reveals the accumulation of NOTCH3 protein in the vessel wall. Although the diagnostic 'gold standard' is DNA analysis, immunostaining also has a high sensititivity and specificity and may be helpful as a diagnostic tool in specific situations.(12)

RADIOLOGICAL FINDINGS

Standard MRI scans of the brain reveal white matter hyperintensities (WMHs) and lacunar infarcts.(4) WMHs are symmetrically distributed and have typical areas of predilection: anterior temporal lobe, frontal lobe, external capsule, internal capsule, brainstem and periventricular white matter. The occipital lobe is relatively spared and the cerebellum is usually not affected. Lacunar infarcts are found in the basal ganglia, thalamus, brainstem and subcortical white matter. T2* weighted gradient echo sequences may reveal cerebral microbleeds, most often in the basal ganglia and thalamus, but also in the brainstem, subcortical white matter and in the cortex.(5) Another MRI finding typical for CADASIL is subcortical lacunar lesions (SLLs).(3) They are believed to be based on dilated perivascular spaces, located at the border between abnormal areas of white matter and cerebral cortex.

The MRI abnormalities are age dependent.(4) WMHs usually appear before clinical symptoms and can be detected from the age of 18 years as small punctuate periventricular or subcortical WMHs, most often starting in the frontal or temporal lobes. With progression of the disease they grow and become confluent up to the point that no normal white matter is visible anymore. Lacunar infarcts appear from the age of 30. Microbleeds appear from the age of 40. In a clinical setting, these MRI abnormalities help recognizing CADASIL.

In a research setting, more advanced MRI techniques have been used to study CADASIL. Volumetric measurements of gray and white matter have demonstrated global brain atrophy as well as hippocampal atrophy in CADASIL.(13;14) Diffusion tensor imaging (DTI) has revealed reduced mean diffusivity and fractional anisotropy of normal appearing and abnormal appearing white matter, suggesting ultrastructural changes in white matter, even before WMHs become visible on conventional MRI.(15) MR spectroscopy has revealed metabolic abnormalities suggestive of axonal injury, myelin loss and gliosis in normal and abnormal appearing white matter as well.(16) Flow and perfusion studies have demonstrated reduced total and regional cerebral blood flow as well as reduced cerebrovascular reactivity in CADASIL.(17;18)

TREATMENT

Currently, no specific treatment for CADASIL is available. The only controlled trial that has been performed in CADASIL showed no effect of the drug Donepezil on the main outcome measure of cognitive impairment.(19) Thus, treatment of CADASIL remains of supportive nature, including physiotherapy, rehabilitation, psychological support and genetic counseling. Pragmatic treatment with anti-platelet drugs, in combination with reduction of vascular risk factors is sometimes used, although the efficacy has not been proven. In order to improve risk factor management, and in order to develop more specific treatment modalities for CADASIL, a better understanding of disease progression and its associated factors is crucial.

DISEASE PROGRESSION IN CADASIL

Cross-sectional studies have shown that in general the clinical symptoms and the MRI abnormalities are more severe in patients with higher age, with MRI abnormalities usually appearing in a characteristic order during the disease.(2;4) Although these studies have provided some insight into the disease course in CADASIL, the ability of cross-sectional studies to assess disease progression and its correlates remains limited.

Three longitudinal studies have been performed about the course of MRI changes and clinical symptoms.(20-22) These studies confirmed that volume of white matter hyperintensities and DTI metrics are progressive in CADASIL and that progression of MRI abnormalities is associated with progression of clinical symptoms. One study found that brain atrophy in CADASIL is progressive in time and is associated with clinical deterioration. However, all these studies have a relative short follow-up time of two years or less, and most of these studies did not specifically search for prognostic risk factors.

An important question in CADASIL is: what is the cause of the remarkable variability in disease progression? Based on cross-sectional studies, no clear cause of this variability has been identified. Associations between disease severity and cardiovascular risk factors have proven to be small and no clinically significant associations with the NOTCH3 genotype have been found.(23) A longitudinal study with a longer follow-up time will be able to more accurately investigate possible prognostic risk factors associated with disease progression.

One prognostic factor of specific interest is cerebral blood flow. In CADASIL, as well as in general small vessel disease, it is often debated whether progression of ischemic changes in the brain is primarily caused by decreased blood flow or by decreased cerebrovascular reactivity. Cross-sectional studies on blood flow have demonstrated that blood flow and

cerebrovascular reactivity are decreased in CADASIL, and that they are both associated with the amount of white matter hyperintensities.(17;18) However, because of the cross-sectional design of these studies, it has been impossible to draw conclusions about the causality of those associations.

Another question regarding disease progression is: what is the radiological substrate of clinical deterioration. For some symptoms such as an acute ischemic stroke episode, it can be assumed that the underlying cause is a single lacunar infarct as can be seen on MRI. However, the cause of other symptoms, such as cognitive dysfunction, is more complex and is incompletely understood. It is unknown whether cognitive dysfunction is mainly caused by WMHs, lacunar infarcts and microbleeds or by atrophy. Longitudinal studies that compare progression of MRI abnormalities with progression of clinical symptoms can help to answer these questions.

It is not known whether disease progression is influenced by factors at the molecular level. Previous studies have not demonstrated genotype-phenotype correlations that clearly affect disease severity or progression. Less common NOTCH3 genotypes, such as homozygosity for a NOTCH3 mutation, could provide some insight into the ways in which genotype may influence disease progression.

HIGH FIELD MRI IN CADASIL

With the arrival of new high-field MRI scanners, it has become possible to study disease processes in the brain in more detail. Two of the advantages of 7 Tesla MRI in the light of CADASIL are its ability to image small blood vessels in more detail, and its increased sensitivity to iron deposition.

The small arteries in CADASIL have been studied only with post-mortem examinations. It is unclear how the abnormalities in the vessel wall lead to impaired blood flow and decreased cerebrovascular reactivity. Loss of smooth-muscle cells, vessel wall thickening and luminal stenosis are three distinct vessel properties that could each independently affect blood flow. Post-mortem studies have confirmed vascular smooth muscle cell loss and vessel wall thickening in all cerebral arterioles.(11) However, the role of luminal narrowing remains unclear, especially at the level of the lenticulostriate arteries. With 7 Tesla MRI it has become possible to visualize the lumina of lenticulostriate arteries in vivo.

Another interesting question is whether CADASIL, a primarily vascular disease, only leads to classical vascular changes, such as infarcts, WMHs, microbleeds, or if other age related

changes also play a role in CADASIL. Previous studies have shown that global atrophy and hippocampal atrophy, characteristics that are generally attributed to Alzheimer disease, are also present in CADASIL.(13;14) From a pathophysiologic point-of-view in CADASIL, but also in small vessel disease in general, it would be interesting to know whether iron deposition, another process usually attributed to degeneration, is also increased in CADASIL.

AIMS OF THIS THESIS

The aims of this thesis are to gain a better understanding of disease progression in CADASIL, by using MRI techniques with standard field strengths (1,5 and 3 Tesla) and to increase insight into cerebral changes in CADASIL by using high field MRI (7 Tesla).

Disease progression

Firstly, we aimed to determine the pattern of progression of MRI abnormalities and identify which of the MRI characteristics at baseline and which of the vascular risk factors, including migraine, are associated with faster disease progression (chapter 2). Secondly, we aimed to determine which MRI abnormalities are the most important substrates of cognitive dysfunction and progressive cognitive decline in CADASIL (chapters 3 and 4) and thirdly, we aimed to determine the relative contributions of total cerebral blood flow and cerebrovascular reactivity to the progression of MRI abnormalities (chapter 5).

To gain insight into the influence or rare genotypes on disease progression, we compared the MRI and symptoms of a patient with a homozygous *NOTCH3* mutation with those of her brother with a heterozygous mutation (chapter 6).

High Field MRI

High field MRI has not been previously performed in CADASIL and we aimed to address the unresolved question whether lenticulostriate arterial lumina are narrowed in living CADASIL patients and if luminal narrowing leads to ischemic changes in the lenticular nuclei (chapter 7). Secondly, we used high-field susceptibility weighted imaging to assess whether diffuse iron deposition is increased in CADASIL, a phenomenon usually attributed to degenerative, rather than vascular, disease (chapter 8).

When applicable, the results of these studies will also be discussed in the light of possible new insights into vascular dementia and migraine in the general population.

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