Magnetic resonance imaging characteristics of CADASIL

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Introduction

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Up to 1991 several families suffering from an autosomal stroke condition of unknown aetiology were reported under various names such as "hereditary multi-infarct dementia", "chronic familial vascular encephalopathy", and "familial disorder with subcortical ischemic strokes, dementia, and leukoencephalopathy"[1-5]. Because of the confusion raised by all these different names, the acronym of CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) was proposed by a French research group in the early 1990s following discovery of the underlying mutation that many of the earlier described families had in common[6-9].

CADASIL is an autosomal dominant disease characterized by migraine, recurrent stroke, and progressive cognitive impairment. This disease is caused by mutations in the *NOTCH3* gene, located on chromosome 19.

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

Clinical aspects of CADASIL

The initial clinical symptoms of CADASIL vary both between and within affected families. Symptoms of this disorder appear from the mid-twenties to around 45 years of age and affected individuals typically die before the age of 65[10].

The most common clinical presentation of CADASIL is the presence of recurrent subcortical ischemic events, which occur in 80% of all patients with a mean age of onset varying from 41 to 49 years. In the early phase of the disease, symptoms are often mild and transient, resembling transient ischemic attacks[8,10,11].

The second most common feature in CADASIL patients is the development of cognitive deficits. Dementia is found in 60% of patients by the age of 45, and in 90% before death[10]. It is characterised by memory impairment and is usually associated with pseudobulbar palsy, gait disturbances, sphincter incontinence and pyramidal signs[8]. It seems that cognitive decline of CADASIL patients can progress in two different ways: a stepwise deterioration due to successive strokes, or the gradual development of a pseudobulbar syndrome[12].

Thirty-five percent of CADASIL patients have attacks of migraine with aura. Migraine with aura is the earliest clinical manifestation, occurring at a mean age of 26[8,10,11,13]. The prevalence of this type of migraine in the general population is about 6%[14]. However, this symptom should suggest a diagnosis of CADASIL only when associated with white matter hyperintensities (WMHs)

on cerebral magnetic resonance (MR) imaging. Remarkably, CADASIL patients often develop migraine attacks shortly before or after their first stroke, suggesting the occurrence of similar pathophysiological events in CADASIL and migraine[12].

Mood and psychiatric disturbances, including severe depression, sometimes with alternating manic episodes, have been observed in 30% of patients with CADASIL[8,10,11]. Like migraine, mood disorders should suggest a diagnosis of CADASIL only when associated with diffuse WMHs on cerebral MR imaging.

Epileptic insults are present in up to 10% of the CADASIL patients and probably are secondary to cortical damage[8,10,11].

A small number of CADASIL patients may experience an encephalopathic illness characterised by a period of impaired consciousness and neurological abnormalities usually recovering after about two weeks[15-17].

Genetic aspects of CADASIL

In 1993 CADASIL was linked to chromosome 19[9,18]. In 1996, mutations in *NOTCH3* gene were found[19]. Until now 54 different mutations have been reported[20]. The highly conserved Notch signalling pathway was originally identified and studied in the fruit fly *Drosophila melanogaster*. The name "Notch" derives from the characteristic notched wing found in flies carrying only 1 functioning copy of the gene. Homozygous *NOTCH3* mutations in fruit fly are lethal, and affected embryos have severe abnormalities, including an excess of neural cells[21]. The Notch signalling appears to function as a general development tool, essential for proper embryonic development in species ranging from insects to mammals. The exact mechanism whereby defects in the NOTCH3 protein cause the vasculopathy of CADASIL remains to be determined. In CADASIL, all mutations in *NOTCH3* are the loss, or gain of a cysteine residue.

Mutation analysis for diagnostic purposes is possible[22]. As intervention to prevent or delay onset age or even change the clinical course of CADASIL is not routinely possible, presymptomatic DNA testing in CADASIL families should be done with caution. DNA testing should be accompanied by genetic counselling, informing the patient and his/her family about the course of the disease and the risk of transmitting the abnormal gene to their offspring's[23,24]. Obviously, attention should be paid to psychological reactions such as denial and minimisation in gene carriers and survivor guilt in non-mutation carriers.

Histopathological aspects of CADASIL

Post mortem studies of affected patients show multiple small infarcts and leukoencephalopathy throughout the subcortical white matter as well as in the basal ganglia and thalamus[2,3,7,25].

The characteristic histological finding is a vasculopathy of small and middle-sized arterioles. Smooth muscle cells of the media are replaced with deposits of basophilic granular electron-dense material known as granular osmiophilic material (GOM) resulting in destruction of vascular smooth muscle cells and fibrous thickening of the arterial wall[7,26].

It is believed that these GOM depositions in the blood vessel wall result in both reduced blood flow and an inability of the blood vessels to regulate blood flow (cerebrovascular reactivity), causing WMHs and lacunar infarcts. Cerebrovascular reactivity reflects the compensatory dilatory capacity of cerebral arterioles to a stimulus such as carbon dioxide or acetazolamide. In elderly individuals impaired cerebrovascular reactivity is associated with WMHs and lacunar infarcts[27-29]. In patients with CADASIL, alterations in cerebral blood flow and cerebrovascular reactivity have also been demonstrated, with a significant reduction in baseline cerebral blood flow and cerebrovascular reactivity in areas of WMHs[30-33]. From these observations, however, cannot be derived whether structural brain changes are secondary to impaired flow, or whether impaired flow is a consequence of brain damage.

Although in CADASIL abnormalities in blood vessels can be found throughout the body, they appear to be most severe in the brain. The vasculopathy in the brain gives rise to the characteristic clinical signs and symptoms in CADASIL patients. The reason for the brain being the site of predilection is still unknown[34].

The diagnosis of CADASIL can be confirmed by electron microscopic (EM) analysis of the arterioles in a skin biopsy[35,36]. Although the identification of characteristic vascular abnormalities (GOM in the media) is highly specific for CADASIL, these abnormalities are not always found. The false negative rate of skin biopsy analysis finding is unknown[37,38].

Radiological aspects of CADASIL

Two types of lesions have been described in patients with CADASIL. The first type are WMHs, symmetrically distributed and located in the periventricular and deep white matter[39]. There is a relative sparing of the arcuate fibers and cortex[40]. The WMHs are predominantly localized in the frontal lobe, followed by the temporal and parietal lobes. The occipital lobe is markedly less severely affected[41,42]. It has been demonstrated that the external capsules and (anterior) temporal lobes are also sites of predilection for WMHs[43]. Brain stem white matter abnormalities, located mainly in the pons and mesencephalon, are also frequently observed, while involvement of the cerebellum appears

to be very uncommon[39,44]. In symptomatic patients MR imaging of the brain is always abnormal, however WMHs have also been detected in asymptomatic *NOTCH3* mutation carriers[45].

The second type of lesions are lacunar infarcts in the centrum semiovale, thalamus, basal ganglia and pons[40]. The prevalence of both WMHs and lacunar infarcts increase with age.

There are several ways to detect in vivo microscopic damage that remains undetected using conventional radiological techniques. Studies using diffusion tensor imaging, magnetization transfer imaging and MR spectroscopy in CADASIL have shown that microstructural changes are present in both normal and abnormal white matter, probably reflecting neuronal loss and demyelination[46-48]. Also, they found that the degree of the underlying ultrastructural alterations is related to the clinical severity.

Differential diagnosis

The differential diagnosis of CADASIL depends upon the age of the patient. The diagnosis of CADASIL is often made at a young age and the recurrence of multifocal neurological deficits with relative young age-of-onset, and WMHs on MR imaging that are initially patchy makes it difficult to distinguish CADASIL from multiple sclerosis (MS)[49,50]. Another differential diagnostic consideration of CADASIL, based on the radiological picture, is mitochondrial encephalopathy with lactic acidosis (MELAS). However, this disease is readily distinguished from CADASIL on the basis of a familial pattern suggestive of maternal inheritance, clinical features, or supplementary tests. Binswanger's disease, a rare form of dementia characterized by loss of memory and cognition, mood changes, and abnormal blood pressure, should be considered in older patients because of the confluent WMHs and lacunar infarcts. However, a history of severe long lasting hypertension is often lacking in CADASIL patients, there is no familial occurrence in Binswanger's disease and the age of onset in Binswanger's disease is usually later.

Purpose and outline of the thesis

The discovery of the mutations in the *NOTCH3* gene in 1996 was an important landmark in CADASIL research since it provides a reliable confirmation of the clinical diagnosis. At the Leiden University Medical Centre (LUMC) a study was started on the clinical, radiological, pathological, neuropsychological, and genetic aspects of CADASIL patients in the Netherlands. Members of 15 unrelated Dutch CADASIL families were asked to participate in this study. Index patients identified through *NOTCH3* mutation analysis were referred from various medical institutions to the LUMC, which serves as a national CADASIL

referral centre. The total number of participants was 63 of which 41 turned out to be mutation carrier and 22 were not. The advantage of this study set-up was that the asymptomatic family members were unaware of their genetic status and a representative control group for the mutated family members was built into the study. The studies that are described in this thesis are based on material that was generated in the Dutch CADASIL study.

The purpose of this thesis is to refine the morphological phenotype of cerebral abnormalities in CADASIL using MR imaging. A diagnosis of CADASIL cannot be made without MR imaging. Recognizing the MR imaging features of CADASIL can help to increase the chance of detecting CADASIL by genetic screening and distinguish this largely underdiagnosed disorder from similar conditions associated with WMHs such as aging, Binswanger's disease, MELAS, and MS. In this thesis we also evaluated the influence of potential risk factors and the effect of the vessel wall pathology on the structural MR lesions.

This thesis addresses the following study objectives:

1) Are cerebral vessels in CADASIL patients more prone to bleed as expressed by the presence of microbleeds?
2) Is there a relation between the amount of microbleeds and disease severity?
3) What is the prevalence and distribution of a type of lacunar lesions that, to our knowledge, has not been described before in the neuroimaging literature in neither CADASIL patients nor in patients with other disorders?
4) What is the typical appearance of MR imaging abnormalities in CADASIL and does this differ and progress per age category?
5) What are the clinical, neuropsychological and radiological features of CADASIL patients under the age of 35 years?
6) Is it possible to distinguishing CADASIL patients from MS patients on the bases of the radiological hallmarks of CADASIL?
7) What is the influence of apolipoprotein E genotype on the development of radiological abnormalities in CADASIL patients?
8) Is a decrease in cerebral blood flow or cerebrovascular reactivity primarily responsible for the development of WMHs and lacunar infarcts?