Staging cerebral amyloid angiopathy: from marker to model

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GENERAL INTRODUCTION

1. General introduction

1.1 Cerebral amyloid angiopathy pathophysiology

1.1.1 The prevalence of cerebral amyloid angiopathy

Cerebral Amyloid Angiopathy (CAA) is one of the main causes of primary intracerebral hemorrhage (ICH) in the elderly. [1, 2] CAA is characterized by the accumulation of the protein amyloid-β in the walls of the cerebral cortical and leptomeningeal vessels and was long thought to be an inconsequential, benign pathological finding of the aging brain. It was only halfway through the 20th century that the pathological finding was recognized for its clinical relevance as a cause of cerebral small vessel disease. Population based pathological studies indicate that CAA is a frequent finding in both demented (50-60%) and non-demented (20-40%) elderly populations in the age range of 80-90 years.[2] In patients with Alzheimer's disease, the prevalence of CAA is even higher and estimated to be present in 85-95% of the cases.[2, 3, 4]

1.1.2 CAA pathophysiology

CAA has a complex and not yet fully understood pathogenesis. In early stages, deposition of amyloid-β in the arterial abluminal portion of the tunica media surrounding the smooth muscle cells and in the adventitia causes vessel wall thickening and reduction of the lumen's diameter. In later stages, this leads to smooth muscle degeneration resulting in thinning, weakening and remodelling of the vessels, and finally in rupture of the vessel wall (see figure 1).[5] The vessels are predominantly affected by the amyloid subtype amyloid-β_{40}, in contrast to the parenchymal amyloid-β plaques in Alzheimer's disease which are mainly composed of amyloid-β_{42}.[6] It is hypothesized that instead of an increase in amyloid-β production as a base for the development of CAA, accumulation of the protein is driven by reduced peptide clearance. However, the exact mechanisms behind amyloid-β accumulation are still largely unknown.[7]

1.1.3 Diagnosing CAA

CAA can only be diagnosed with certainty via histopathological examination of brain tissue. In order to be able to diagnose the disease during life, the Boston criteria were developed in the 1990s (and have since then been modified repeatedly) to diagnose 'possible' and 'probable' CAA based on a combination of clinical symptoms and MRI features (table 1).[8-10] The Boston criteria are a widely used clinical tool and have paved the way for a much broader range of (image based) CAA research. Over the years, the criteria have been modified to implement new

Figure 1: CAA histopathology.

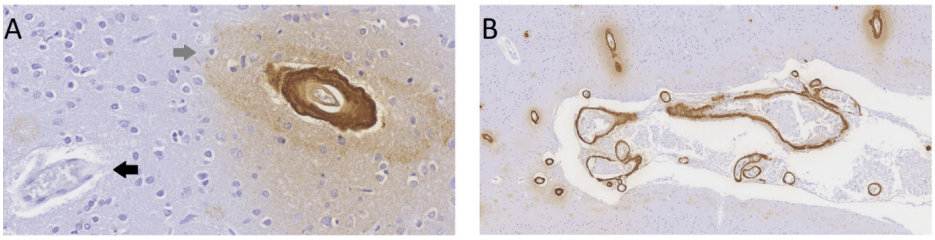


Figure 1A: example of a healthy vessel (black arrow) and a vessel with CAA, vessel wall thickening and remodelling (grey arrow). Figure 1B: example of multiple cortical and leptomeningeal vessels with CAA.

discoveries, leading to the recent formulation of an updated version: the Boston criteria 2.0.[10] Currently the MRI markers that are part of the Boston criteria version 2.0 are strictly lobar, cortical or cortico-subcortical macrobleeds and microbleeds, cortical superficial siderosis, convexity subarachnoid hemorrhage, and white matter features (enlarged perivascular spaces in het centrum semiovale and white matter hyperintensities in a multi-spot pattern). These MRI markers, as well as the clinical symptoms, will be discussed in more detail below (see sections 1.2 and 1.3).

1.1.3 Hereditary Dutch-type CAA

Although most patients with CAA suffer from non-hereditary sporadic CAA, a few hereditary variants exist. The best documented of these genetic variants is hereditary Dutch-type CAA (D-CAA), previously called Hereditary Cerebral Hemorrhage With Amyloidosis Dutch-type (HCHWA-D) or 'de Katwijkse ziekte'. D-CAA originates from a coastal village in the Netherlands and is caused by an autosomal dominant mutation at codon 693 of the Amyloid Precursor Protein (APP) gene on chromosome 21, which leads to accumulation of amyloid-β in the cortical and leptomeningeal arteries; histopathologically similar to sporadic CAA.[11, 12] Patients with D-CAA usually present with the same clinical symptoms as patients with sporadic CAA, but have an earlier onset and a more severe disease course.[13] D-CAA can be diagnosed with certainty via genetic testing for the causal mutation in the APP gene, and as it is pathologically similar to sporadic CAA, it is often used as a unique genetic model for sporadic CAA, in which early, presymptomatic disease stages can be investigated.[14, 15]

1.2 Clinical CAA: a spectrum of symptoms

1.2.1 Clinical manifestations of CAA

The most well-known clinical manifestation of CAA is ICH. CAA usually has a severe

Table 1: The Boston Criteria version 2.0 for Cerebral Amyloid Angiopathy.[10]

Definite CAA	Probable CAA with supporting pathology	Probable CAA	Possible CAA
Full brain post-mortem examination, demonstrating: • Spontaneous ICH, TFNE, cSAH or cognitive impairment/ dementia • Severe CAA with vasculopathy • Absence of other diagnostic lesion	*Clinical data and pathological tissue (evacuated hematoma/ cortical biopsy), demonstrating:* • Presentation with: spontaneous ICH, TFNE, cSAH or cognitive impairment/ dementia • Some degree of CAA in specimen • Absence of other diagnostic lesion	*Patient aged ≥50, clinical data and MRI demonstrating:* • Presentation with: spontaneous ICH, TFNE, cSAH or cognitive impairment/ dementia • At least 2 of the following: strictly lobar hemorrhagic lesions on MRI in any combination: ICH, CMB, foci of cSS or cSAH OR • One lobar hemorrhagic lesion plus one white matter feature (severe CSO-EPVS or WMH in a multisport pattern) • Absence of deep hemorrhagic lesions • Absence of other cause of hemorrhagic lesions • Hemorrhagic lesion in cerebellum not counted as either lobar or deep hemorrhagic lesion	*Patients aged ≥50, clinical data and MRI demonstrating* • Presentation with: spontaneous ICH, TFNE, cSAH or cognitive impairment/ dementia • Absence of other cause of hemorrhage • One strictly lobar hemorrhagic lesion on MRI: ICH, CMB, cSS, cSAH OR • One white matter feature (severe CSO-EPVS or WMH in a multisport pattern) • Absence of deep hemorrhagic lesions • Absence of other cause of hemorrhagic lesions • Hemorrhagic lesions in cerebellum not counted as either lobar or deep

ICH: intracerebral hemorrhage. TFNE: transient focal neurological episodes. cSAH: convexity subarachnoid hemorrhage. CMB: cortical microbleed. cSS: cortical superficial siderosis. CSO-EPVS: enlarged perivascular spaces in the centrum semiovale. WMH: white matter hyperintensities.

disease course with an ICH recurrence rate higher than that of all other ICH causes: previous studies found an annual ICH recurrence risk of 7.4% per year for patients with CAA-related ICH and 1.1% in patients with CAA-unrelated related ICH.[13, 16, 17] CAA is also a known cause of cognitive impairment and vascular dementia.[16, 18] A third possible presentation of CAA are Transient Focal Neurological Episodes (TFNE). TFNE are defined as transient, stereotyped, recurrent attacks strongly related to cortical superficial siderosis on MRI.[19, 20] Early definitions of TFNE described only somatosensory symptoms, however the definition has been extended and currently

encompasses temporary disturbances in motor, somatosensory, visual, and language dysfunction.[21] The prevalence of TFNE is not yet clear: a previous multi-center study described TFNE in approximately 15% of patients with sporadic CAA, yet it is possible that this prevalence is in reality higher as TFNE are not always recognized in clinical practice.[16, 20] Lastly, a subset of patients with CAA present with an inflammatory subtype of CAA, CAA-related inflammation (CAA-ri). CAA-ri is clinically characterized by rapidly progressive cognitive decline, seizures and headache, as well as by signs of inflammation on MRI.[22] CAA-ri is relatively rare, however as patients with CAA-ri respond well to immunosuppressive therapy, early diagnosis is important.[16, 23] By investigating the presymptomatic disease phase in patients with D-CAA, the earliest signs and symptoms of CAA can be uncovered, which might lead to a better understanding of disease pathophysiology. One of these possible early symptoms is migraine with aura. It has long been known that there is a relation between migraine, migraine aura and cerebrovascular disease, although the exact pathophysiological basis for this is not yet fully understood.[24, 25] Although migraine has been reported in sporadic CAA, its exact prevalence and characteristics, as well as whether it is a possible early sign of the disease, is yet unknown.[26]

1.2.2 Management of CAA

Current management of CAA is mostly based on decreasing ICH recurrence risk and, if possible, managing symptoms; there is no method available for prevention or treatment of CAA itself. To decrease risk of ICH (recurrence), clinicians are advised to avoid use of antithrombotic drugs if possible in patients with lobar ICH or lobar microbleeds.[27, 28] Furthermore, in patients with hypertension and CAA it has been shown that antihypertensive medication also reduces the risk of ICH recurrence.[28-30] The only proven effective symptom treatment in CAA is the use of immunosuppressive medication for the inflammatory subtype of CAA; CAA-ri.[23] In the search for a treatment for CAA itself, it is often hypothesized that reducing vascular amyloid-β load by using monoclonal amyloid-β antibodies could improve vascular dysfunction in CAA. Although some trials in Alzheimer's disease and one study in patients with sporadic CAA showed promising results, use of these antibodies is not without risk, as several trials found that use of these antibodies can trigger CAA-like manifestations, either inflammatory or hemorrhagic.[31, 32] Better biomarkers for CAA could possibly aid in the identification of patients at risk for these severe side effects. Although future research looks promising, current clinical practice does not yet have any clear treatment for patients with (hereditary) CAA.

1.2.3 Disease modifying factors in CAA

Patients with CAA show a striking variability in disease course. Age at first symptomatic ICH, ICH recurrence rate and ICH location, prevalence of cognitive impairment and vascular dementia and survival differ strongly between patients.[16, 18, 33] Even in patients with D-CAA, who share the exact same causal mutation, there are large differences in clinical phenotype regarding age at disease onset and disease progression: previous studies found that age at first ICH ranges from 39-70 years and the number of ICH recurrences during life varies between 1 and 10.[34-36] This variability suggests that there are factors that influence CAA disease progression. One known modifying factor in sporadic CAA is *APOE-e* genotype.[37, 38] Previous research has shown that the *APOE-e4* allele appears to enhance vascular amyloid-βand is associated with sporadic CAA without ICH, whereas the *APOE-e2* allele seems to promote structural vasculopathic changes in amyloid-β -laden vessels which can lead to vessel rupture and is associated with ICH and disseminated cSS.[18, 33, 39] Although there is evidence for the role of *APOE-e* genotype in sporadic CAA, no clear evidence for an important role in D-CAA has been found sofar.[40] One of the other possible explanations for the variability in disease course in CAA could be the effect of sex. The only available studies in CAA patients are a study in D-CAA from the nineties, which found a higher mortality rate in females compared to males with D-CAA, and a study on sex differences in primary ICH, which found that females more often have lobar hemorrhages compared to males.[36, 41] In mouse models of CAA, it has been found that female sex is associated with more cortical microbleeds and more severe CAA pathology.[42, 43] In patients with Alzheimer's disease, another amyloid-β based disease in which patients often have co-existent CAA, the role of sex has been more widely investigated.[44] Alzheimer's disease is far more prevalent in females than in males; females have been reported to make up almost two-thirds of patients with Alzheimer's disease.[45, 46] Furthermore, females with the disease seem to have a higher Alzheimer pathology load, including parenchymal amyloid-β deposition, compared to males.[46-48] Lastly, APOE-e4 seems to give greater Alzheimer's disease risk for female compared to male carriers.[49, 50] These findings suggest that sex might impact pathogenic pathways for amyloid-βdeposition in Alzheimer's disease. Further observational studies have shown that estrogen depletion influences Alzheimer's disease onset, and that estrogen replacement therapy might enhance cognitive function in females with Alzheimer's disease and might reduce the risk of developing the disease in healthy females.[51-53] These studies have led to the formulation of the 'estrogen hypothesis', which states that estrogen might be protective against Alzheimer's disease related dementia, and that dysfunction of the hormone

exacerbates the disease process in females.[54, 55] To test this hypothesis several trials on hormone replacement therapy in Alzheimer's disease are currently ongoing in different centers around the world.[55-57] This possible association between sex and amyloid-β deposition in the vessel wall could also be present in patients with CAA, but as of yet there is no clear evidence for the role of sex in CAA.

1.2.4 CAA and deep perforating arteriopathy

Cerebral small vessel disease (cSVD) is thought to encompass a spectrum of diseases, with CAA and deep perforating arteriopathy (DPA), another frequent cause of ICH, on opposing ends. DPA is strongly related to hypertension and is therefore also called hypertensive arteriopathy. Whereas CAA causes mostly lobar located lesions, DPA is characterized by lesions mostly localized in the 'deep' areas of the brain (basal ganglia, thalamus, brainstem).[58] Differentiation between these two cerebral angiopathies is important as it influences clinical decision making (for example regarding the more rigid contra-indication for anticoagulant medication in patients with CAA) and prognosis (CAA has a higher ICH recurrence rate compared to DPA).[58] Patients who show signs of both deep (possibly DPA-related) and lobar (possibly CAA-related) small vessel disease are said to have mixed type small vessel disease.[59] At the moment it is thought that mixed type small vessel disease is driven by vascular risk factors similar to DPA, but with an ICH recurrence rate higher than patients with pure DPA and lower than patients with CAA related ICH, and an amyloid-β load comparable to patients with DPA.[59, 60] More research is necessary to determine the implications of these findings and whether they should influence clinical decision making in these patients.

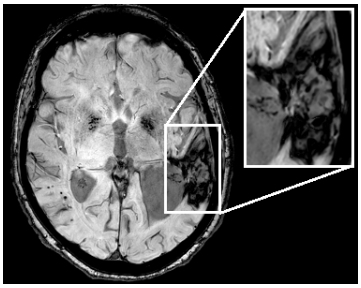
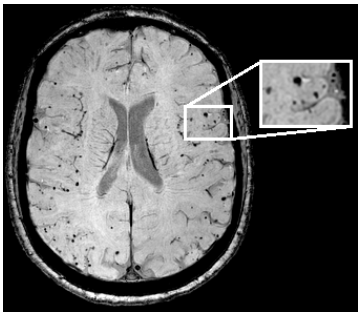
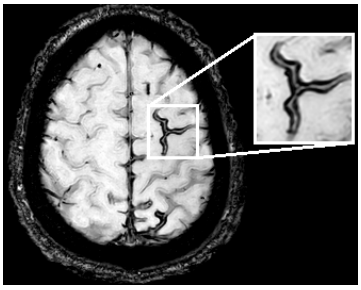
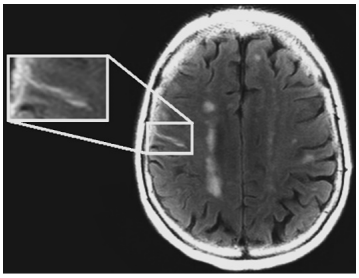
1.3 Neuroimaging in CAA: the importance of MRI

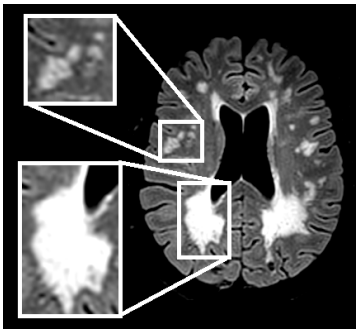
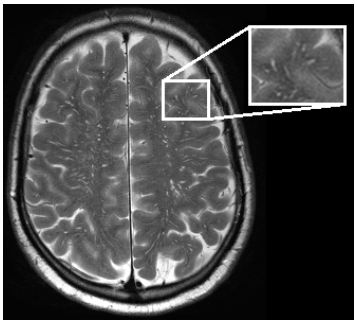
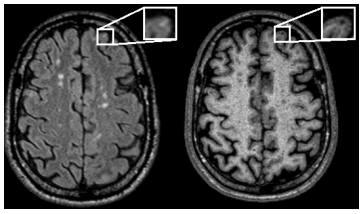
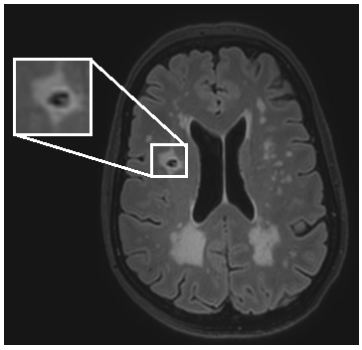
1.3.1 MRI markers of small vessel disease

MRI is the current gold standard of investigating SVD status and progression and is therefore an important factor of CAA research. MRI enables in vivo monitoring of CAA disease progression and severity, and is a non-invasive method for investigating early as well as late stages of the disease. CAA and other cSVD are characterized by hemorrhagic and non-hemorrhagic markers on MRI. In 2013 the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) criteria have been developed in order to create consensus regarding the definitions and imaging standards for CSVD related neuroimaging markers.[61,62] Although many of the markers discussed in the STRIVE criteria occur throughout the spectrum of CSVDs, several of the markers are thought to be more specific for CAA, and location or pattern of CSVD markers

differentiate between various CSVD subtypes.[60] Table 2 gives an overview of the CSVD MRI markers and their locations most widely acknowledged to be associated with CAA.

Table 2: Overview of CAA related CSVD markers on MRI.

MRI marker	Definition according to the STRIVE criteria[61,62]	CAA related location	Example
Macrobleed	Areas of low signal with associated blooming seen on T2, T2*-GRE or SWI sequences, usually with irregular shape and/or with a cystic cavity. Larger than microbleeds (usually >10mm).[61]	Lobar cortical or cortico-subcortical	
Microbleed	Well-defined, small round or oval areas of homogeneous low signal with associated blooming, seen on T2*-GRE or SWI.[61]	Lobar cortical or cortico-subcortical	
Cortical superficial siderosis	Hemosiderin depositions in a curvilinear pattern following the cortical surface, which can be detected using T2*-GRE or SWI sequences.[62]	Supratentorial	
Convexity subarachnoid hemorrhage	Hyperintense signal on fluid-attenuated inversion recovery (FLAIR) images, with or without a corresponding hypointensity on T2*-GRE or SWI sequences, filling the sulcal space.[63]	Supratentorial	

White matter hyperintensities (WMH) and subcortical white matter spots	Bilateral, mostly symmetrical focal and/or confluent hyperintensities on FLAIR or T2-weighted sequences, can appear as isointense or hypointense on T1-weighted sequences.[61] Also small spots of WMH in the subcortical regions.[64, 65]	Periventricular and deep	
Enlarged perivascular spaces	Small, sharply delineated structures of cerebrospinal fluid (CSF) intensity seen on T2-weighted images, measuring <3mm in cross-sectional diameter, following the course of perforating vessels, round if in axial and longitudinal if cut in the long axis of the perivascular space.[61,66]	Centrum semiovale	
Cortical microinfarct	Lesions that are hypointense on T1-weighted images, <4 mm in diameter, restricted to the cortex, perpendicular to the cortical surface, and distinct from perivascular spaces and microbleeds.[67,68]	Cortex	
Lacunes	Round or ovoid, subcortical, fluid-filled cavity (signal similar to CSF) of between 3 mm and about 15 mm in diameter, hyperintense on T2-weighted images, hypointense on T1-weighted images, and hypointense on FLAIR images with a surrounding rim of hyperintensity.[68]	Lobar	

The two most well-known MRI markers of CAA, microbleeds and macrobleeds, are thought to be two separate entities, each with their own pathophysiology.69 Although the terms 'micro' and 'macro' suggest that the lesions are subdivided according to size, the STRIVE criteria applies caution with regard to size of lesions on T2*-GRE or SWI sequences as the susceptibility artefacts depends on field strength and acquisition parameters. The criteria do state that microbleeds are usually 2-5mm in diameter with a maximum of 10mm, thereby assuming that hemorrhages with an irregular shape and/or a cystic cavity which have a size of <10mm are rare. However, in our clinical practice we often see these sort of lesions in patients with CAA, although the prevalence and the volume distribution of hemorrhages in CAA are not yet known. Possibly the most clinically relevant MRI marker for CAA is cortical superficial siderosis (cSS), as it is one of the main predictors for CAA progression and (lobar) ICH.[70, 71] Much is still unknown about the pathophysiology of this MRI marker. It is hypothesized that cSS represents the chronic phase of acute convexity subarachnoid hemorrhage, caused by acute, repetitive or perhaps chronic leakage from leptomeningeal vessels into the subarachnoid space. [63, 72] Further investigation of the pathophysiology of cSS is necessary as it could contribute to a better understanding of the pathophysiology of CAA overall. Although it used to be unclear if the cerebellum was an area affected by CAA, recent studies have shown that hemorrhages in the superficial cerebellum (the cerebellar cortex and vermis) are associated with CAA.[73, 74] This indicates that vessel fragility caused by amyloid-β accumulation also takes place in the vessels supplying the superficial cerebellum. It is not yet known whether this is also the case for the leptomeningeal cerebellar vessels, nor whether other CAA related MRI markers such as cortical superficial siderosis can also occur in the cerebellum.

Next to these structural MRI lesions, previous studies have shown that patients with sporadic CAA and D-CAA have impaired cerebrovascular reactivity.[75, 76] In these studies cerebrovascular reactivity is measured using functional MRI to observe vascular response in the occipital lobe to a visual stimulus. This decrease in cerebrovascular reactivity to a visual stimulus was even found in presymptomatic patients with D-CAA who did not yet have any other sign or symptom of the disease.[75] The theory behind this finding is that amyloid-β which has deposited in the vessel wall of the cerebrovasculature reduces the ability of the vessel to dilate upon stimulation, causing a decreased dynamic vessel response.[75] The discovery of new CAA related MRI markers, both in early and late phases of the disease, is of the utmost importance in CAA research as it aids diagnosing CAA in cases of uncertainty and increases the overall understanding of CAA pathophysiology. Furthermore, novel markers need

to be found which can be used to monitor disease status as well as the effect of possible, future treatments. In this search MRI plays an important role.

1.3.2 MRI developments and 7 Tesla MRI

Over the years the field of MRI has advanced with development of new techniques, optimization of sequences and development of MRI scanners operating at high(er) field strength. In current clinical practice the use of 3.0 Tesla MRI is favored over the use of 1.5 Tesla MRI in patients with CAA, as higher spatial resolution and increased contrast to noise ratio enables better visualization of small vessel disease related lesions such as microbleeds and perivascular spaces.[77] Currently several studies have been performed which use ultra-high field 7 Tesla MRI to investigate cerebral anatomy and microvascular structures in healthy subjects as well as in different pathologies.[78-81] 7 Tesla MRI allows for a more detailed analysis of anatomical features and vascular structures, making it an ideal method for investigating more subtle radiological signs of small vessel disease such as cortical microinfarcts and for investigating possible novel markers.[80, 82-84] The use of 7 Tesla MRI has also led to new questions and challenges: the system is not yet validated for clinical use, and shows such detailed images that it requires additional training to differentiate between what is normal anatomy at high field 7 Tesla and what is possible pathology. Additionally, many of the clinical criteria based on imaging (such as the Boston criteria) have been developed based on lower field MRI and have not been validated at 7 Tesla MRI. Despite these challenges, 7 Tesla MRI is a valuable asset in the search for novel biomarkers for CAA.

1.4 Current challenges in CAA

The field of CAA research faces several challenges. Firstly, there are still many parts of the CAA pathophysiology which are yet unknown: the natural disease course including early stages, the variability in disease onset and disease course between patients and the possibility of the existence of different phenotypes within CAA are all questions which need to be answered for a better understanding of the disease with as an ultimate goal to find possible leads for an effective treatment. Secondly, a major difficulty in the search for a treatment for CAA is that there is no ideal established bio-marker to monitor disease progression in vivo and herewith treatment effectiveness, especially in the early phase of the disease course. Thirdly, research in the early phases is difficult as patients with the sporadic variant usually present in a late, symptomatic stage.[85] This emphasizes the need for further research in the hereditary variants of CAA, in which these early stages can be investigated.

1.5 Aims and outline of this thesis

In this thesis we investigated novel clinical and radiological markers of hereditary and sporadic CAA. **Part I** of this thesis focusses on the clinical characteristics of patients with D-CAA and sporadic CAA. In Chapter 2 we investigated the presence of migraine with aura and its clinical relevance as an early clinical marker in patients with D-CAA. In Chapter 3 we investigated possible sex differences in patients with sporadic CAA and D-CAA, focusing on onset, disease course and radiological markers. In Chapter 4 of this thesis we investigated possible mechanisms behind the sex differences found and described in Chapter 3, using autopsy data. We investigated sex differences in CAA prevalence in a cohort of at risk individuals, and investigated the effect of sex on factors known to contribute to hemorrhaging (leptomeningeal grade III vessel remodelling and CAA load) in a different cohort, containing participants with definite CAA.

Part II of this thesis describes several novel MRI markers and their clinical relevance in patients with D-CAA and sporadic CAA, using both 3 Tesla and 7 Tesla MRI. In Chapter 5 we investigated the prevalence of two possible novel 7T MRI markers, intragyral hemorrhages and a striped occipital cortex sign, in patients with D-CAA. In Chapter 6 we investigated the prevalence of these two novel markers found and described in Chapter 5, in patients with sporadic CAA. In Chapter 7 we described a novel marker, CSF hyperintensities, discovered at non-contrast 7T FLAIR in participants with CAA. We investigated the prevalence and temporal dynamics of CSF hyperintensities and their relation with cSS at non-contrast 7 Tesla MRI in participants with CAA and controls. In Chapter 8 we investigated the prevalence and characteristics of another novel marker, cerebellar superficial siderosis, at 3 Tesla MRI in patients with D-CAA and sporadic CAA. In Chapter 9 we investigated hemorrhage size and volume distribution at 3 Tesla MRI in patients with D-CAA and sporadic CAA, introducing a new hemorrhage class, 'the mesobleed'.

Part III, the last part of this thesis, consists of Chapter 10 in which we combined all available data regarding CAA biomarkers and their temporal ordering to create a pathophysiologic framework for CAA disease progression. Finally, in Chapter 11 of this thesis, we used cross-sectional data from patients with presymptomatic and symptomatic D-CAA to investigate the temporal ordering of biomarkers in CSF and on MRI.

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