Staging cerebral amyloid angiopathy: from marker to model

Koemans, E.A.

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SUMMARY
NEDERLANDSE SAMENVATTING
ABBREVIATIONS

Summary

Cerebral Amyloid Angiopathy (CAA) is one of the main causes of intracerebral hemorrhage (ICH) in the elderly, and affects millions of people worldwide. CAA is caused by the deposition of the protein Amyloid-β in the walls of the cerebral and leptomeningeal vessels, which leads to vessel fragility and eventually rupture. CAA has a variable disease course and can present with a spectrum of symptoms. Diagnosing CAA during life is difficult, as for a definite diagnosis can only be made based histopathological analysis of the brain tissue. However, the Boston criteria have been developed in order to make a 'probable' or 'possible' CAA diagnosis during life, based on clinical presentation and MRI markers. Although most patients with CAA suffer from non-hereditary, sporadic CAA (sCAA), a few hereditary variants exist. The best documented of these variants is hereditary Dutch-type CAA (D-CAA, also called HCHWA-D or 'de Katwijkse ziekte'). D-CAA is caused by an autosomal dominant mutation in the APP gene, and patients have an earlier onset and more severe disease course compared to patients with sCAA. D-CAA is pathologically similar to sCAA and is therefore often considered a genetic model for sCAA in which it is possible to investigate the early, presymptomatic phases of the disease.

The aim of this thesis was to investigate novel clinical and radiological disease markers for D-CAA and sCAA, thereby giving new insights into CAA pathophysiology, searching for tools to aid CAA diagnosis and investigating ways to measure disease severity and progression.

Part I of this thesis focusses on the clinical characteristics of patients with CAA. In Chapter 2 we add a new symptom of CAA to the clinical spectrum of the disease by showing that migraine with aura can be an inaugural symptom of hereditary Dutch-type CAA (D-CAA). We found a prevalence of migraine with aura in D-CAA mutation carriers which was far higher than in the general population (51% of men and 59% of women with D-CAA, all with visual aura, compared to 13% of men and 33% of women in the general population), and showed that migraine attacks were usually an early sign of the disease, preceding the first symptomatic hemorrhage in 77% of the carriers. Furthermore, onset of migraine on or before the third decade was associated with an earlier onset of the first hemorrhage (mean age 49y vs 56y). Based on these data we conclude that migraine with aura can be an early sign of D-CAA, demonstrating that in the presymptomatic phases of the disease there are already pathological processes at work which increase the susceptibility of patients with D-CAA for cortical spreading depression. Further prospective studies are necessary to investigate the role of migraine in sCAA, and to further unravel the pathophysiology of this symptom.

In **Chapter 3** we investigated sex differences in D-CAA and sCAA, using two cohorts of prospectively collected clinical and radiological data from participants with sCAA and D-CAA. We found that males with CAA seem to have an earlier onset and more hemorrhagic disease course compared to females. In **Chapter 4** of this thesis we further investigated the effect of sex on CAA, by looking into sex-differences in histopathological biomarkers for CAA. Using a cohort containing autopsy data of patients with cognitive impairment we did not find a difference in the prevalence of CAA between males and females, but did find that females had more often parenchymal amyloid-β compared to males. In another cohort, containing autopsy data of histopathologically confirmed clinical sCAA patients, we investigated cortical iron load, as a marker for hemorrhage load, in males and females with sCAA. Here we found an association of female sex with a higher prevalence of parenchymal amyoid-β, but no sex differences related to vascular amyloid-β. Furthermore, in a cohort of patients with definite sporadic CAA, we found a higher microbleed count but lower cSS proportion in females compared to males, with a higher overall local cortical iron burden in males. Based on these results we conclude that the sex differences described in **Chapter 3** of this thesis are most likely not due to differences in global CAA severity between male and female patients with CAA, but may be caused by more complex factors such as vascular remodeling. We furthermore conclude that larger datasets of patients with definite CAA are necessary to further investigate these more complex processes.

Part II of this thesis focusses on novel radiological markers for sCAA and D-CAA. In **Chapter 5** we discovered two novel markers at high-field 7 Tesla MRI in patients with D-CAA: the striped occipital cortex and intragyral hemorrhages. Both markers were only seen in patients with symptomatic D-CAA; intragyral hemorrhages in 47% and a striped occipital cortex in 40% of patients, and not in presymptomatic patients or in healthy controls. In **Chapter 6** of this thesis we investigated the frequency of occurrence of both novel markers on 7 Tesla MRI in patients with sCAA as well as in patients with ICH not caused by CAA but by deep perforating arteriopathy (DPA). Here we discovered that both markers can be present in sCAA, although more rarely than in D-CAA: intragyral hemorrhages were present in 12% and a striped occipital cortex in only 3% of the patients with sCAA, but in none of the patients with DPA related ICH. Intragyral hemorrhages could in retrospect also be identified at 3 Tesla MRI. The absence of these markers in patients with DPA related ICH seems to suggest specificity for CAA. In **Chapter 7** of this thesis we investigated CSF hyperintensities at non-contrast 7 Tesla MRI and the relation of this phenomenon with cSS. We discovered that this marker is prevalent in 71% of participants with sCAA and 46% of participants with D-CAA. In 54% of the cases there was complete overlap of the CSF hyperintensities with cSS, 46% of the participants, however, had at least one sulcus of CSF hyperintensities which did not overlap with cSS. The new marker

showed variability at 2 year follow-up: most patients demonstrated increase of the number of foci with CSF hyperintensities, however 17% of the participants had at least one focus with CSF hyperintensities at baseline which was no longer visible at 2-year follow-up. We hypothesize that this dynamic marker is a possible sign of subtle leakage of protein and/or blood products in the CSF. Chapter 8 of this thesis describes a new CAA-related MRI marker at 3 Tesla MRI; cerebellar superficial siderosis (SS). Cerebellar SS was found in 10% of the participants with symptomatic D-CAA and in 9% of patients with sCAA, and in none of the patients with DPA related ICH. We consider the cerebellar SS we found in patients with CAA to be different from infratentorial superficial siderosis (iSS), a phenomenon unrelated to CAA and previously described in literature. We did not find cerebellar SS in presymptomatic patients with D-CAA and therefore conclude that it is a relatively late marker of CAA. In Chapter 9 of this thesis we investigated hemorrhage size distribution in sCAA and D-CAA, especially focusing on hemorrhages that share characteristics with both microbleeds (size < 10mm) and macrobleeds (irregular shape and/or containing a cystic cavity), which we called mesobleeds. We found that mesobleeds are frequently present in patients with D-CAA and sporadic CAA and have a different diameter and volume distribution compared to micro- and macrobleeds. Therefore we conclude that these bleeds should be scored separately from micro- and macrobleeds.

In the last part of this thesis, part III, we bundled all available knowledge regarding disease biomarkers for CAA, both based on an extensive literature search as well as on our own data, to form a pathophysiological framework for CAA disease course in Chapter 10. Within this framework we formulated four different pathophysiological disease stages: step 1). Initial vascular amyloid-β deposition, step 2). Alteration of cerebrovascular physiology, step 3). Appearance of non-hemorrhagic brain injury, and finally step 4). Appearance of hemorrhagic brain lesions. In Chapter 11, the final chapter of this thesis, we explored the merit of this framework by investigating the proposed biomarkers and their temporal ordering in presymptomatic and symptomatic participants with D-CAA.

Conclusion

This thesis has investigated novel clinical and radiological (MRI) markers of CAA and has used them to formulate a pathophysiologic framework for the temporal ordering of disease processes in CAA. CAA is a disease with a complex disease cascade and a large variety in disease course, both clinically and radiologically. However, it is just this variety that gives hope for the future: if we find what drives variability in CAA we might find ways for disease modification, prevention and treatment, and identification of in vivo biomarkers with specificity for CAA are a vital part of this search.