Microbleeds in Dementia

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'We know accurately only when we know little, with knowledge doubt increases.'

Johann Wolfgang von Goethe

General Discussion

Objective

In this thesis we aimed to gain novel insights into the radiological construct of MBs in dementia in relation to: I clinical relevance, II underlying vasculopathies and associated pathologies and III novel imaging techniques.

In this chapter, the main observations are summarized and reviewed in the context of the current knowledge. Subsequently, in order to aid interpretation, methodological issues will be addressed. Finally, the possible clinical implications of our findings are presented, together with recommendations for further research.

Summary and interpretation of main findings

Part I Clinical Relevance

Several former studies did not find any associations between MBs and cognition in AD patients,[1, 2] in contrast to non-AD populations, often with higher MB burdens.[3-6] Possibly, most AD studies were hampered by insufficient power as they did not include enough cases with a substantial number of MBs to measurably add to the effects on cognition of advanced neurodegenerative disease. We therefore took a different approach, attempting to maximize the supposed MB associated effect. We did this

by selecting the top 5% of AD patients, regarding MB burden, from our database and compared these patients with age and sex matched AD patients without MBs. We found a clear difference in global cognition as measured with the crude MMSE scale between these groups (chapter 2.1). These effects remained after correction for atrophy measures and white matter hyperintensity (WMH) severity.

The findings of this proof-of-principle study supported our hypothesis that MBs have a deleterious effect on cognition. In addition, we demonstrated earlier, that multiple MBs in AD patients were associated with higher all cause mortality.[7] Taken together, one may hypothesize that AD patients with MBs show a more aggressive disease course characterized by a rapid cognitive decline and shorter survival. This assumption led us to assess whether MBs could also predict faster subsequent cognitive decline, as little was known about the predictive value of MBs in established AD regarding the subsequent disease course. To evaluate this hypothesis, we studied a large sample of AD patients with a relatively long mean follow-up of 3 years. We observed no relation between baseline MBs and rate of decline (chapter 2.2). We therefore concluded that MBs were not associated with a more rapid AD course. Probably survival of AD patients does not relate to more rapid neurodegeneration, but rather to other causes of mortality like fatal strokes for example. Indirect support for this notion comes from a study in over 400 "vascularly enriched" elderly subjects, in which multiple MBs were indeed found to be associated with increased mortality due to cardiovascular and hemorrhagic stroke, based on their location.[8]

Although prevalence of MBs in AD and risk factors have been investigated, data on occurrence of new MBs from longitudinal studies in AD were lacking. Studying MB incidence is important for several reasons. First, the known risk factors were mostly derived from cross-sectional studies and longitudinal assessment may provide more evidence for any causal relationships. Second, since trials with amyloid-lowering therapy reported occurrence of incident MBs, an ample need arose for data on the natural MB incidence in AD. We studied a cohort of over 250 memory clinic patients with a mean follow-up of approximately 2 years. We found a two-year incidence of one or more new MBs of 12% (same estimate in total population and in AD patients only; chapter 2.3). Baseline and incident MBs were not associated with cognitive decline

over time. Determinants predicting incident MBs were MBs at baseline, but also MRI signs of small vessel disease, i.e. WMH grade and lacunar infarcts, predicted incident MBs. This was more prominent for nonlobar MBs, whereas smoking related more to strictly lobar MBs. In addition APOE ε2, a risk factor associated with CAA related hemorrhage, was also associated with incident MBs.

From these studies concerning the relevance of MBs in dementia, we may conclude that MBs or the underlying pathology they represent, can contribute to cognitive deficits, when severe enough. It is debatable however, whether the subtle effects on cognition of one or a few MBs are relevant when the devastating effects of advanced AD pathology are already present. This is indirectly supported by the observation that in most studied populations, for example healthy elderly or stroke survivors, a relation between MBs and cognition has been observed, but typically not when AD is diagnosed.

Part II Underlying vasculopathies and associated pathologies

The findings of two studies in part I already hinted at a possible relation between MBs and amyloid pathology. In the first study (chapter 2.1) we found that the CSF levels of AD patients with multiple MBs were lower than in AD patients without MBs. Decreased CSF levels of are generally held to reflect increased intracerebral amyloid deposition.[9] Whether increased amyloid deposition in AD patients with MBs, as indicated by CSF abnormalities occurs mainly in plaques or in cerebral small vessels, known as CAA, is not known. Furthermore, we found that both APOE ε4 (chapter 2.1) and APOE ε2 (chapter 2.3) were related to MBs. In addition to the consistently observed predominantly lobar MB pattern in our AD patients, these genetic findings may further support a relationship of these MBs with CAA. Moreover, a study in sporadic non-demented CAA patients, with large intracerebral hemorrhages (ICH), which usually presents without significant amyloid plaques, corroborated our CSF findings, showing that CSF levels of and Aß40 were both decreased compared with controls and even with AD patients, suggesting intravascular amyloid deposition.[10] In contrast to AD patients, where is the predominant peptide found in plaques, in sporadic CAA, Aß40 is predominantly deposited in vessel walls. Additionally, Aß40

levels in plasma have been found to be higher in patients with signs of small vessel disease.[11] We therefore set out to study levels of both amyloid peptides in CSF and plasma, at the same time assessing blood-brain barrier (BBB) integrity as measured by albumin ratios in AD patients with and without MBs, but also in patients with vascular dementia (VaD; mostly with MBs), using patients with subjective complaints without MBs as controls. In this study (chapter 3.1) we replicated our previous observation, by showing that MBs in AD were associated with additional decreases in CSF levels in an independent sample with any number of MBs. However, no relation between MBs and Aß40 levels was found in AD. This may be explained by a less advanced stage of CAA, known to be associated with less Aß40 deposition relative to ,[12] or alternatively by a different subtype of CAA in AD. In VaD subjects however, CSF levels of and also Aß40 were decreased, whereas in plasma Aß40 levels were non-significantly increased, together with signs of BBB dysfunction, which seems to suggest leakage from CSF to the circulation. Subsequently, in the PET study, we zoomed in on the BBB function using verapamil (chapter 3.3). We did not find any differences in P-glycoprotein transporter function between AD patients with and without MBs. The finding that MBs in AD are not associated with any measurable BBB changes, may thus provide validation for previous studies using amyloid imaging in relation to MBs, which neglected the possibility of BBB effects. Finally, we had the opportunity to directly link the clinical observation of high numbers of MBs on MRI during life to post-mortem evaluation in a case study. We evaluated a case with rapidly progressive dementia and multiple "stroke-like" or "seizure-like" episodes, with innumerable MBs at MRI as most prominent imaging abnormality, suggesting CAA. In the absence of major pathology related to AD, other dementias or macroscopic infarcts or hemorrhages, this clinical and radiologic diagnosis was neuropathologically confirmed and further refined as severe capillary CAA with dyshoric changes and multiple microinfarcts with and without surrounding iron depositions. Extending on the conclusions of part I, this case, again as a proof-of-principle, showed that not only cognitive deficits, but even severe dementia may arise from a vascular amyloidopathy, diagnosable during life using MB pattern on MRI, notably in the absence of other pathologies explaining the decline. Furthermore, this case provided direct neuropathological evidence that even without classic plaques, (peri)vascular amyloid can result in measurable CSF

changes. This may suggest that the extremely low CSF amyloid levels in AD patients with MBs, reported in part II, indeed partially reflect vascular deposition of amyloid.

From the multi-disciplinary evidence presented in this part, we conclude there is a robust link between (lobar) MBs and amyloid pathology in dementia. In addition, we found no measurable effects reflecting BBB dysfunction associated with MBs in AD, potentially rendering arterial sampling obsolete in these patients, although this may differ for VaD patients.

Part III Novel techniques in microvascular imaging

From studies in parts I&II, we have concluded that MBs in an abundant quantity may relate to cognition and are associated with amyloid pathology, especially when their location is lobar. These findings stress the importance of accurate MB detection in diagnosing, following and experimentally treating memory clinic patients.

In chapter 4.1 we found that the new SWI post-processing method detected more MBs than the conventional method at the same scanner in the same patients at the same time. No substantial differences in associations with imaging and patient characteristics were found however. Another technical development, which has been shown to be highly sensitive in detecting MBs is ultra-high field strength MRI.[13] In a sample of young AD patients, 7T scanning did not reveal significantly more MBs compared with 3T, although stronger relations of MBs with age and APOE ε4 were observed, indicating clinical relevance of the additional lesions. Probably, the gain in MB detection of ultra-high field and SWI imaging, does not reflect artefacts, but rather reflects true consequences of an underlying bleeding-prone vasculopathy.[14] This is further supported by findings in an elderly population, reporting risk factors of patients with MBs on an advanced technique were more similar to those of patients with MBs on conventional scanning than patients without MBs.[15] The additional MBs seen with the advanced technique only, were not associated with any of the studied risk factors, however. Moreover, the total MB load at the advanced scanning technique in that study was found to predict future MBs more accurately, supporting the concept of a true underlying bleeding-prone vascular state. Findings from our work and of

others may suggest that several of these new techniques in MB detection, may therefore earlier identify patients with potentially relevant vascular disease.

Another consequence of cerebral microangiopathy are pathologically defined microinfarcts, which have been found to be related with cognition during life, but unfortunately are not visible using conventional neuroimaging.[16, 17] At 7T, microinfarcts have been visualized, but pathological confirmation is still scarce. Since 7T has very limited availability, we pragmatically used 1.5T post-mortem imaging, enhanced with a quantitative technique, in our attempt to detect neuropathologically defined MIs or associated tissue changes. In this pathologic-radiologic correlation study, we found no effects of MIs on tissue properties assessed by T1 relaxation time mapping in AD cases. In the non-AD cases with signs of small vessel disease however, MIs related to a different aspect and size of the confluent white matter hyperintensities, suggesting a relation with more severe small vessel disease. We concluded that a 1.5T field strength may be too low to detect the subtle changes reflecting MIs and that higher field strengths may be needed for their detection.

From the studies in part III, we may conclude that both post-processing technique and higher field strengths result in more sensitive detection of MBs. The lack of apparent discrepancies of the clinical relevance of MBs between these new and the conventional techniques, further underlines the robustness of the concept of MBs as readily defined using conventional techniques. The clinical value of MB detection however, may not be easily translated or extrapolated from conventional imaging to new techniques and should thus be established carefully, whenever a new technique is being introduced. Regarding microinfarcts, we can conclude that a moderately high field strength is not suitable for microinfarct detection in AD, even when assessed by advanced quantitative techniques.

Methodological considerations

Selection of patient population

MBs have most consistently been found to be associated with age.[18] As a specialized center focused on patients with early onset dementia, we attract many young patients.