

Microvascular contributions to dementia

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KNOWLEDGE VALORIZATION

The general aim of this thesis was to investigate whether microvascular dysfunction in the form of blood-brain barrier (BBB) disruption is associated with cerebrovascular lesions and common markers of Alzheimer disease (AD), and how these markers are associated with cognitive performance in memory clinic patients and older individuals with normal cognition. This valorization paragraph describes the societal relevance and potential implementation opportunities of the results.

Relevance

Dementia is a major cause of progressive cognitive and functional decline in older people and as such forms a serious threat to individual and public health. Around 40 million people are currently living with dementia, and the largest risk factor for the disease is age. With the increasing life expectancy of populations all over the world, the number of people with dementia is expected to double over the next 20 years. Alzheimer disease (AD) is the most common cause of dementia, contributing to an estimated 70% of cases. Importantly, although scientific advances over the past decades have significantly increased our understanding of the biological processes underlying AD, all clinical trials that target amyloid deposits have failed and there is currently no effective treatment available that delays the onset or slows down the progression of the disease.

One of the major challenges with regard to the development of AD treatment strategies is the multifactorial and heterogeneous nature of the disease. The key neuropathological hallmarks of AD include amyloid plaques and neurofibrillary tangles, but their pathophysiological cause remains unknown and the current view is that there is likely more than one factor contributing to the abnormal protein accumulation and associated cognitive decline. In this light, there is growing evidence that cerebrovascular damage plays a critical role in the development and progression of the disease. AD and vascular disease share many risk factors and multiple neuropathological and neuroimaging studies have shown that mixed brain pathology (neurodegenerative and vascular) is the most frequent finding in cases with dementia. A better understanding of the role of cerebrovascular damage in AD will probably facilitate the future development of successful healthcare interventions aimed at halting disease progression.

The studies in this thesis focus on the most frequent cause of cerebrovascular pathology in older individuals with AD, which is cerebral small vessel disease (cSVD) due to hypertensive vasculopathy (HV) and/or cerebral amyloid angiopathy (CAA). Previous research suggests that an

important underlying mechanism of both types of cSVD is blood-brain barrier (BBB) disruption, which refers to the failure of strict transport regulation from blood to brain and vice versa at the capillary level. BBB disruption may lead to leakage of toxic plasma components which probably results in cellular damage. Dysfunction of the BBB may at the same time disrupt waste product clearance from the brain. However, the extent of BBB dysfunction and associated pathology in aging and AD remains poorly understood. The studies in this thesis aid in clarifying the role of BBB leakage in cSVD and AD and provide basic insights into the possible clinical and pathological consequences of cSVD-related BBB leakage in normal aging and in memory clinic patients.

Main findings

The findings in the present thesis suggest that damage to the microvascular network in the brain negatively and independently affects brain health. More specifically, the research in this thesis suggests that dysfunction of the BBB along the continuous cerebrovascular endothelium in the brain is related to imaging markers of ischemic and hemorrhagic cerebrovascular brain damage and slower cognitive performance in individuals with and without cognitive impairment.

In the first study described in this thesis we found that cSVD severity is related to hippocampal neurodegeneration in individuals with early AD, but not in individuals with dementia or in the absence of cerebral amyloid pathology. This finding suggests that cerebrovascular disease is associated with neurodegenerative processes at an early disease stage when the brain is vulnerable due to co-existent AD pathology.

Next, we measured BBB dysfunction in living humans using two different magnetic resonance imaging approaches. With dynamic contrast-enhanced MRI we identified a positive association between BBB leakage in the cerebral gray and white matter and cSVD severity, which was in turn associated with a decline in processing speed performance in memory clinic patients and cognitively normal older individuals. With delayed post-contrast FLAIR imaging we identified small pericortical leaks of contrast agent into the cerebrospinal fluid in approximately 20-40% of the investigated study population. This type of BBB dysfunction was positively associated with age and MRI signs of old ischemic stroke. These findings demonstrate that subtle age- and/or cSVD related BBB dysfunction can be measured with these two MRI techniques, and provide novel insights into the role of BBB dysfunction in relation to cerebrovascular pathology and cognitive decline in older individuals.

Finally, we explored the association between hemorrhagic brain pathology and BBB dysfunction in a systematic review analysis and a *post mortem* MRI-histopathology study. In these studies we found support for the hypothesis that cSVD-related BBB dysfunction is a possible mechanism involved in the etiology of cerebral microbleed and intracerebral hemorrhage formation.

Target groups and implementation opportunities

The results of this thesis are of direct interest to researchers that examine the role of microvascular disruption in dementia and researchers in the cSVD and AD field in general. Our findings suggest that cerebrovascular disease can independently contribute to neurodegenerative processes at an early AD stage, which underlines the importance of incorporating cerebrovascular damage when studying AD. Moreover, the results in this thesis show that BBB leakage of contrast agent throughout the cerebral tissue and at small pericortical foci is associated with ischemic and hemorrhagic cerebrovascular damage and slower information processing speed in memory clinic patients and cognitively normal individuals. These findings expand current insights into the role of cerebrovascular damage in older individuals with and without cognitive impairment and open doors to further research on this topic

The results are also of direct interest to neuroradiologists that encounter post-contrast enhancement on FLAIR images in older individuals without a known neurological cause of BBB disruption. Our results suggest that contrast agent leakage into the CSF is probably common in older individuals with and without cognitive impairment, and as such should not be confused with severe conditions that may cause pericortical enhancement such as meningeal metastasis.

Also, the results in this thesis can be of interest to pharmaceutical companies who seek to find treatment strategies and biological (imaging) readouts with the aim of reducing cerebrovascular brain pathology and slowing down cognitive decline. Enhancing BBB integrity may form a possible target for future treatment that could slow down processing speed deterioration and cSVD-related brain damage. This will be relevant for individuals with AD and cSVD, but also to healthy older individuals at risk for cerebrovascular brain pathology due to age-associated BBB leakage. Should future research establish a cause-effect relationship between BBB leakage and hemorrhagic brain pathology, then the DCE-MRI and post-contrast FLAIR imaging techniques could be helpful for the identification of individuals at risk for hemorrhagic brain pathology and in the assessment of treatment response in future trials that target BBB integrity.

Innovation and future directions

The research described in this thesis further establishes a significant role of cerebrovascular abnormalities in AD, which has been identified in previous neuropathological and imaging studies. We expand this knowledge by showing that cSVD is an independent contributor to neurodegeneration in individuals with early AD. Moreover, we used two contrast-enhanced MRI techniques that are still very new in the aging and dementia research field. We applied dynamic contrast-enhanced MRI in individuals with and without cognitive impairment and for the first time performed BBB leakage analyses in the brain tissue with almost whole brain coverage, relating this to performance on tests for specific cognitive domains. In addition, we were the first to describe the appearance of pericortical enhancement on post-contrast FLAIR images in a substantial proportion of individuals with mild cognitive impairment and dementia, and to demonstrate pilot data showing that these small foci of contrast agent extravasation are of chronic nature in this study population. Furthermore, we summarized the currently available literature on BBB leakage as a possible important factor in the etiology of cSVD-related brain hemorrhage and contribute empirical evidence of an association between cerebral microbleeds and BBB leakage in *post mortem* tissue of CAA patients.

Before the results in this thesis can be of practical use, future research is necessary to further disentangle the complex associations between BBB dysfunction, cerebrovascular brain pathology, neurodegenerative pathology and cognition in older individuals. Longitudinal studies in larger samples that measure BBB dysfunction, cSVD markers, neurodegeneration, cognitive performance and amyloid pathology concurrently are needed to shed light on these complex associations and the temporal sequence of pathological events. Moreover, longitudinal studies that monitor BBB dysfunction with MRI in populations at risk for future hemorrhage, such as individuals with CAA, will shed light on the utility of BBB dysfunction measured with contrast-enhanced MRI as a maker for hemorrhage risk and as future target for the development of hemorrhage prevention strategies. Further refinement of the DCE-MRI technique would be of great interest since the technique in its current state is prone to noise and can be applied only to monitor subtle BBB leakage in subject groups but not at the individual level.