Microvascular and blood-brain barrier dysfunction in Alzheimer's disease

Valorization Addendum

Healthcare problem

Alzheimer's Disease (AD) is the most common cause of cognitive decline and dementia in the elderly in the developed world. It is characterized by an insidious onset and slow deterioration of cognitive function, progressing until death. The impact of AD on daily life is enormous, both for the patient and loved ones. Increasing standards of living and healthcare also increases the prevalence of AD in developing countries as people live longer, and it is estimated that in 2040 roughly 90 million people worldwide will suffer from AD, making it a global healthcare problem.

Despite the fact that AD has been identified and investigated since 1906, research efforts still have not been able to find the cause of AD, nor is a cure currently available. The main focus of AD research has been the accumulations of insoluble proteins amyloid ß causing plaques, and τ causing tangles in the brains of patients with AD. However, treatments aimed at preventing or removing the plaques and tangles have so far not yielded a proper treatment for the symptoms of AD. Furthermore, biomarkers which aim for early diagnosis of AD, have so far shown mixed results, and sensitively and reliably diagnosing AD at an early (presymptomatic) state is not possible. This has prompted some researchers to search for alternate explanations that might cause AD. One of the most promising candidates is vascular pathology. It has been shown that patients exhibiting pure AD without vascular pathology are rare, and many risk factors have a vascular component or basis. A prime suspect for vascular pathology in the brain is the neurovascular unit, a structure located in the microvascular wall and unique to the brain, which is specialized to support and protect neuronal function.

Main findings

The main results of this thesis is that different elements of the neurovascular unit are damaged in AD. The blood-brain barrier is an important part of the neurovascular unit which strictly regulates transport between the blood and brain tissue. Using Dynamic Contrast-Enhanced (DCE) MRI, the blood-brain barrier was found to be impaired in AD, allowing small contrast agent molecules to leak out of the blood space. Although the consequences of the blood-brain barrier impairment are currently unclear, the uncontrolled passage of substances into the vulnerable brain parenchyma is very likely to be harmful. The research in this thesis also aims to assist future research, as possible

improvements to the DCE-MRI sequence and analysis have been investigated, making it more sensitive to the subtle blood-brain barrier leakage found in AD. Combining the DCE-MRI technique with Arterial Spin Labeling (ASL) MRI not only showed that patients with an early stage of AD exhibit cerebral hypoperfusion, but that the hypoperfusion is also linked to the blood-brain barrier leakage severity. Given that local perfusion is also regulated by the neurovascular unit, this shows that AD affects multiple elements of the neurovascular unit, and that the neurovascular unit impairment is progressive.

Another aspect of cerebrovascular pathology are White Matter Hyperintensities (WMHs), which are a common finding on brain MRI images of patients with AD. WMHs are considered to represent vascular pathology, and often exhibit local pathological effects such as demyelination. Using diffusion MRI, the research in this thesis has shown that the WMHs exhibit a direct effect on the hippocampal white matter bundles connecting the hippocampi with different gray matter regions. Specifically, it was found that WMHs cause an enlargement of the white matter tracts going through them. This indicates either a pathological swelling of the white matter tracts, or a compensation mechanism where white matter fibers are rerouted to avoid WMHs. Both hypothesized mechanisms could have a detrimental effect on information transfer speed, and consequently cognitive function.

Combined, the research in this thesis provides additional evidence and possible pathways for cerebrovascular pathology in AD. Although the exact pathways through which AD develops or causes cognitive decline and dementia are still unknown, any knowledge on the complicated pathological cascade of AD will help finding new treatments, prevention methods, or biomarkers for early diagnosis.

Target population

The main targets of the results of this thesis are researchers aiming to further investigate the underlying pathological processes responsible for AD. The results provide new targets for investigation, which will have to be researched in future studies, as most of the results are based on limited numbers of patients, using novel and experimental techniques. This thesis also contains new neuroimaging and analysis techniques which can be applied not only in AD, but also in other neurodegenerative diseases such as small vessel disease and multiple sclerosis. With the information provided in this thesis, improved techniques can be developed which are less burdening and more sensitive, to further study AD.

The current results are also important for the general population, as anyone is at risk of developing AD. This thesis has provided further evidence for a vascular component of AD, but a cure or prevention method will require much more research. Still, if the role of vascular pathology in AD receives more attention, awareness of the importance of vascular health at a stage before AD symptoms arise will increase. A better vascular health for the general population will not only decrease the amount of vascular diseases, but may also help combat the symptoms of AD. An awareness campaign for the importance of vascular health to prevent dementia is likely to reach a large portion of the population, given the broad interest in AD. This is evident from the amount of attention AD gets in the media. For example, when the results of Chapter 3 were published, the Radiological Society of North America issued a press release which was widely shared by international media outlets. This shows a global interest in AD, and in particular novel starting points, which can be capitalized upon.

Innovation and future directions

The innovative aspect of this thesis is that novel neuroimaging methods were applied to investigate microvascular pathology in AD. This required adaptation of existing methods and advanced analyses to increase sensitivity, as AD is a progressive disease showing very subtle pathological changes in early stages. Given the results, the methods are proven to be feasible to detect group differences, but the neuroimaging methods applied in this thesis require improvement before clinical integration is possible and useful. Further application of the dual time resolution DCE-MRI sequence will elucidate the role of the blood-brain barrier in AD. Mainly, the results of the current thesis should be replicated in larger patient groups and in longitudinal studies to assess age-dependent effects. Also, the links between AD, cognitive decline, vascular pathology, and the blood-brain barrier should be further investigated. Furthermore, investigating the reproducibility of the DCE-MRI protocol is necessary to confirm that the method is reliable before clinical application can be considered.

The DCE-MRI protocol may also be useful to develop pharmaceuticals that target the brain. Because the blood-brain barrier very tightly regulates the passage of molecules from the blood into the brain, drugs that target the brain may also be stopped, which poses a challenge for the development of new drugs. Certain techniques may be used to temporarily open the blood-brain barrier to allow for the passage of drugs, such as the use of high-intensity focused ultrasound. DCE-MRI may be applied to validate these techniques and to measure their effectiveness.

Improvements to the dual time resolution DCE-MRI sequence should include decreasing the scan time, increasing the spatial coverage of the fast portion of the protocol, decreasing the noise and imaging artefacts and improving the analysis to incorporate more physiological parameters to better model the in vivo conditions. Currently, the measured concentration differences and blood-brain barrier leakage rates are very small. As is shown in Chapter 4, improvements to the DCE-MRI sequence are both necessary and possible. If it is sufficiently improved and the reproducibility of the technique has been proven, DCE-MRI will be able to provide a truly quantitative measurement of blood-brain barrier leakage. The clinical application of the DCE-MRI protocol may include the ability to distinguish between a healthy and a non-healthy brain at risk for AD on an individual basis. Other possible future uses of the DCE-MRI protocol may be to evaluate the effectiveness of treatments for the BBB, and to provide a general overview of cerebrovascular health to help monitor potential vascular risk factors.