Imaging blood-brain barrier function in aging

Impact paragraph

Main findings

The main goal of this thesis was to see whether we could support the notion that blood-brain barrier (BBB) disruption may be an underlying mechanism of normal age-related decline and a contributing factor to cognitive aging. Therefore, we investigated whether older individuals have more BBB leakage, even when healthy, and whether higher BBB leakage is then paired with more normal age-related cognitive decline. To detect the subtle leakage values that occur in normal aging, we used dynamic contrast-enhanced magnetic resonance imaging (DCE MRI). In this technique, a contrast agent is injected into the blood stream during scanning, so that the amount of contrast spreading from the blood to the brain can be measured

We found that BBB leakage in the white matter was significantly higher in older individuals. The association between BBB disruption and age was strongest in those brain regions known to be especially vulnerable to age-related deterioration, namely the brain regions involved in higher-order cognitive functions. Moreover, higher BBB leakage in the white matter was paired with significantly stronger decline in memory retrieval. These relations already being detected in people who age without overt cognitive or neurological impairment, supports the notion that BBB disruption may be an initiating factor of age-related pathology and one of the age-related brain changes contributing to cognitive impairment in older individuals.

To validate the technique, we applied DCE MRI to the circumventricular organs (CVOs). These small structures do not have a BBB, as their main function is to regulate the communication between the blood, cerebrospinal fluid (CSF) and brain. We could detect significantly positive contrast transfer in the CVOs, and introduced dynamic contrast-enhanced MRI as a promising method to investigate CVO permeability characteristics to better understand how pathogens could enter the brain through these structures.

To elaborate on other systems important for homeostasis in the central nervous system (CNS) and potentially involved in age-related impairment, namely the glymphatic system and the blood-CSF barrier (BCSFB), we conducted two review studies. The glymphatic system is a waste clearance system in which CSF is exchanged with interstitial

fluid to clear solutes from the interstitial space. In the first review study, we concluded that BBB transport and glymphatic clearance are complementary clearance systems with partially overlapping mechanisms to provide a well-balanced neural environment. The second review study showed that contrast-enhanced MRI can also be used to measure BCSFB disruption, while this has received less attention than measuring BBB disruption. The BCSFB determines the composition of the CSF and also influences homeostasis in the CNS. New techniques to measure glymphatic clearance or BCSFB leakage are being developed, for instance techniques that can detect even very low contrast concentrations in the CSF.

Relevance

People do not only want to reach older ages, they want to reach these ages in a healthy manner. However, many people fear they will experience declining mental health, in particular cognitive decline, as they get older. This emphasizes the relevance of determining what factors influence how much cognitive decline someone will experience over time. We have now obtained evidence that there is indeed a role for the BBB, as people who experienced more cognitive decline over the years were shown to have more BBB leakage. BBB disruption seems to be present before the emergence of disease or disability or overt brain pathology, and could be a promising target for interventions aimed at improving vascular health and promoting successful aging.

For the time being, however, interventions that repair BBB leakage to prevent age-related decline are under development, but not yet available. Still, indicating BBB disruption as contributor to cognitive aging has scientific relevance and can provide us with new study directions. We could for instance investigate BBB breakdown and cognitive changes over time, to obtain more information on the causal relations, or see whether health interventions that aim to promote successful brain aging are in part mediated by BBB disruption, and how this subsequently relates to cognitive decline. In the future, BBB leakage rate might even be used as a biological outcome measure to evaluate the effectiveness of such interventions. Moreover, our findings could also be an incentive to develop methods to prevent or reverse BBB damage.

BBB disruption is not only present in dementia, but already associated with cognitive decline in normal aging individuals, which implies that it may occur very early in the process of neurodegeneration. Alzheimer's disease and Alzheimer pathology used

to be seen as separate from vascular dementia and vascular pathology. Lately, however, it has become understood that both forms of pathology are overlapping and additive or interacting processes and may have a common trigger. The BBB is part of the vasculature and BBB disruption is strongly involved in vascular pathology. Moreover, the BBB is important for the removal of the amyloid-β protein from the brain, and accumulation of this protein is an important hallmark of Alzheimer's disease. Being an early event in neurodegeneration and being associated with both vascular and Alzheimer pathology, suggests that BBB disruption may possibly be a common trigger for age-related brain pathology.

Our findings have conceptual relevance and emphasize that knowledge on vascular mechanisms should be integrated with knowledge on Alzheimer mechanisms, as these mechanisms are not separate processes, but influence each other. Many intervention studies have primarily focused on removal of the amyloid-β protein from the brain. Future studies, however, should also focus on barrier integrity and vascular health. The general public is mostly aware that vascular risk factors, such as high blood pressure, high fat diet, physical inactivity or high cholesterol, increase their risk of cardiovascular disease. It is much less known that, or how, these vascular risk factors can also influence our brain health. Although our specific findings should be further investigated and validated before being communicated to the general public, we have recently obtained a better general understanding of the link between vascular damage and brain pathology. The general public could be made more aware that risk factors for cardiovascular disease may also put them at risk of neurovascular disease and neurodegenerative disorders.

In a broader perspective, any disruption in barrier function or impairment in waste clearance system can disturb the chemical balance in the brain tissue, which can be very detrimental to neuronal functioning and lead to a variety of pathological processes, such as inflammation or hypoxia. Not only dementia is accompanied by such a disturbance in homeostasis, but conditions such as sleep disorders, traumatic brain injury and stroke are characterized by an imbalance in the brain fluid dynamics. Gaining more knowledge on barrier function during aging and neurodegeneration and finding new ways of measuring barrier function may be proven useful for a much wider range of conditions.

Target group

First of all, our findings can be an incentive for further research and can therefore be important for other researchers, such as neuroscientists. The findings need to be further elucidated, for instance by establishing the causal relations between BBB disruption, other types of brain pathology and cognitive change. Furthermore, interventions to prevent or reverse BBB damage should be developed and investigated. These interventions can range from lifestyle changes to protect vascular integrity to biological interventions, such as restoring NAD^+ levels, which has been demonstrated to protect BBB integrity. Our findings can also be of interest to MR physicists. In particular, the BBB leakage measurement requires further standardization to design a method that can be uniformly applied across various research sites. The method also requires improvement of the detection sensitivity to very low concentrations of (extravasated) gadolinium-based contrast agent. We have also mentioned the emergence of new techniques to image glymphatic clearance or BCSFB leakage. Further developing and implementing these techniques may offer exciting new research opportunities.

BBB disruption may become a valuable target for aging research. Not only can it lead to disturbance in homeostasis of the CNS and contribute to a wide range of disorders, it may also be an underlying mechanism of cognitive decline in normal aging individuals. Moreover, BBB disruption seems to occur before neurovascular pathology or other types of brain pathology become visible. While our findings specifically are more relevant to the scientific community than to the general aging population, the public could be made more aware that their vascular health, and lifestyle choices that affect their vascular health, may influence their chances of successful aging. In creating this kind of awareness lies an important task for the government, whose responsibility it is to advice and inform the general public through health campaigns.

Dissemination activities

Our findings have been spread throughout the scientific community by publications in scientific journals and presentations at scientific conferences (Cerebral Vascular Biology conference 2019, International Society for Magnetic Resonance Imaging conference 2020). They fit in a growing research interest into the role of vascular factors in neurodegeneration and support the notion that, besides accumulation of the amyloid-β protein, studies into Alzheimer's disease should focus on neurovascular dysfunction.

Recently, the Alzheimer Center Limburg has executed an awareness campaign to inform the general public that healthy behaviors, for instance related to diet and physical exercise, can improve their brain health (WeZijnZelfhetMedicijn.nl). These types of behaviors target vascular risk factors, and our findings emphasize the vascular contribution to brain health. Our findings therefore support the necessity of such a campaign, which can in turn help to communicate the general message supported by our findings to the general public, for instance through media or community participation.