Novel insights in the pathophysiology of cerebral small vessel disease

APPENDIX

VALORISATION

VALORISATION

Life expectancy is increasing in our current society, as well as health, social and economic burdens that come along with it. Stroke and dementia are two major examples of ageing-related disorders. Annually, 15 million people worldwide suffer a stroke. Of these, 5 million die and another 5 million are left permanently disabled, placing a burden on family and community.[1] In Europe, the annual economic cost of stroke is an estimated €27 billion: €18.5 billion for direct costs and €8.5 billion for indirect costs. An additional €11.1 billion is calculated for the value of informal care.[2] Worldwide, around 50 million people have dementia, and there are nearly 10 million new cases every year. The total number of people with dementia is projected to reach 82 million in 2030 and 152 million in 2050. Dementia is one of the major causes of disability and dependency among older people worldwide. Dementia has a physical, psychological, social, and economical impact, not only on people with dementia, but also on their carers, families and society at large. In 2015, the total global societal cost of dementia was estimated to be US$ 818 billion, and with our ageing society, these costs are expected to rise continually on a global level.[3] Cerebral small vessel disease (cSVD) is a disorder involving the small vessels in the brain. It is considered the underlying cause of lacunar stroke, which forms twenty per cent of all strokes. Moreover, cSVD is a major contributor to cognitive impairment and dementia.[4] So far, no effective treatments exist for cSVD. Treatment of lacunar stroke is focused on cardiovascular risk reduction.[1] However, this mainly targets the later stages of the disease when the initial damage is already done. In the care for patients with dementia, providing information and long-term support is the only care that is available. Currently, there are no therapies to cure dementia or to alter its progressive course.[3] In order to develop effective treatments for stroke and dementia, a better understanding of the pathophysiology of cSVD is indispensable.

One of the challenges in cSVD research is that cSVD is a chronic disease and it takes years if not decennia for the disease to evolve from its initial stages to the stage with clinical symptoms. To understand the disease in depth, studies in all stages are essential. As cSVD is not associated with acute mortality, in vivo studies in especially the early stages are not easily performed. So far, in vivo studies using conventional imaging techniques have provided a fairly amount of information on the processes occurring in cSVD. However, to acquire a more in depth understanding of the pathophysiology, more advanced methods are needed. Quantitative dynamic contrast-enhanced (DCE) MRI, intravoxel incoherent motion (IVIM) MRI and intravital microscopy are advanced imaging techniques that may enhance our knowledge of cSVD.

Using DCE-MRI, we quantified the blood-brain barrier leakage in patients with cSVD and healthy controls. Our observations confirmed that blood-brain barrier leakage was associated with cSVD and that this leakage occurred in the white matter as well as cortical grey matter. These results underlined diffuse endothelial dysfunction in cSVD. Using IVIM MRI, we found

that higher microvascular blood flow was associated with cognitive function in patients with cSVD compared with controls, suggesting a direct link between blood flow and cognition. Furthermore, capillary dysfunction appeared to relate to patients with cSVD. These findings provide more insights in the pathophysiology of cSVD.

In addition, by proposing a dysfunctional neurovascular unit as the underlying cause of cSVD, we provide future directives in the research of cSVD. As so many processes appear to play a role in the pathophysiology of cSVD, it is desirable to look at these processes as an entity. This approach may elucidate the interactions between the processes and as such provides a better understanding of cSVD.

In various ways, our study contributes to a better understanding of cSVD, supports the development of new imaging techniques and their analysis and interpretation, and sets a path for further research. Although this is not a direct valorisation for society at this very moment and the imaging techniques have no clinical value yet, this knowledge may eventually lead to the development of effective diagnostic means and treatments of cSVD, enabling early detection and stabilization or even cure of cSVD, which in turn may alleviate the socio-economic burden that stroke and dementia impose on our society.

1. WHO. Global burden of stroke. http://www.who.int/cardiovascular_diseases/resources/atlas/en/.
2. Di Carlo A. Human and economic burden of stroke. *Age Ageing*. 2009;38:4-5
3. WHO. Dementia. http://www.who.int/news-room/fact-sheets/detail/dementia.
4. Pantoni L. Cerebral small vessel disease: From pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol*. 2010;9:689-701