Cerebral small vessel disease

ADDENDUM

IMPACT PARAGRAPH

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This thesis focussed on cerebral small vessel disease (cSVD) and aimed to improve current knowledge on the pathophysiological processes in the neurovascular unit (NVU), beyond classical ideas of hypoperfusion, in cSVD. Furthermore, we aimed to gain more insights in the systemic character of cSVD. Consequently, the results of this thesis are not solely of interest to neuroscientists, but to a larger scientific and clinical audience as well. Besides, it also has societal relevance, especially when keeping in mind the ageing society in Western countries and the increasing societal requirements on participation and independency. In the following sections, the relevance and (potential) impact of the research performed in this thesis will be discussed.

Scientific relevance

In the last two decades, studies using conventional brain imaging techniques have provided quite a lot of information on the processes that contribute to the development of cSVD. However, conventional imaging techniques can only provide information about the end-stage (macrostructural) consequences of microvascular dysfunction to the brain tissue, but do not provide a direct measure of microvascular function. As such, the exact pathophysiology of cSVD remains poorly understood. By making use of different advanced imaging techniques, we acquired a more in depth understanding of the processes involved in the pathophysiology of cSVD.

This research serves as a foundation for future studies on cSVD. The results of this thesis underline the importance to investigate multiple aspects of the NVU concomitantly to better understand the complex pathophysiology of cSVD. Even more important, the acquired knowledge in this thesis can be used to develop future therapies, that can target multiple aspects of the NVU simultaneously, thereby preventing disease progression more efficiently. Our findings also support the use of advanced imaging techniques for monitoring treatment response directly at the NVU level, instead of downstream radiological or clinical effects which may take long time, thereby providing important surrogate endpoints in clinical trials. Moreover, NVU dysfunction has also been proposed in the pathogenesis of several neurodegenerative diseases, including for example Alzheimer's disease and Parkinson's disease.[1] We have provided a framework for approaching the NVU that may be useful not only for cSVD research, but for other neurodegenerative disorders as well.

We provided further evidence for cSVD to be part of a multi-system disorder of the small blood vessels. Our results provide important directions for future research: (I) shared mechanistic pathways between small vessel diseases in different organs should be prioritized, and (II) clinical trials should be extended to test benefits not only to the brain but to multiple organ systems.

Lastly, the research in this thesis has been conducted within the framework of the CRUCIAL consortium. Collaboration with cardiologists and pre-clinical researchers in this consortium has led to cross-fertilisation of ideas and results, and creation of a lot more data that are still open to being analysed. Next to that, our research shows that it is possible to implement complex and advanced brain imaging techniques at different sites. This might encourage the development of international consortia of expert centres in order to boost research in cSVD.

Future healthcare and societal relevance

Cerebral small vessel disease (cSVD) is a prevalent and impactful disease: it majorly contributes to cognitive impairment and dementia, and is also considered the underlying cause of a significant amount of ischemic strokes and deep intracerebral haemorrhages. Dementia and stroke are common. Currently more than 55 million people live with dementia worldwide with nearly 10 million new cases yearly,[2] and over 12.2 million people worldwide suffer a stroke annually.[3] Moreover, both dementia and stroke are major causes of disability and dependency worldwide, and are associated with a high amount of healthcare resource utilization and costs. As such, the estimated global costs of dementia were 1.3 trillion US dollars in 2019, and the estimated global cost of stroke were over 721 billion US dollars in 2017.[2-4] Both dementia and stroke are ageing-related disorders, and are associated with the presence of cardiovascular risk factors. With the increasing life expectancy, and increasing rates of obesity and type 2 diabetes, the prevalence of stroke and dementia, and the social and economic burden that come along with it, can only increase in the future. As such, research efforts to get grip on one of the most prevalent causes of aging related cerebral disorders are most relevant.

There is an unmet need for improved management of cSVD. Early detection and prevention of cSVD are important. Nonetheless, currently, diagnosis of cSVD is made at the stage that damage has already been done: the patient suffered a stroke or presents with cognitive impairment, and the brain scan shows macrostructural abnormalities. However, as cSVD is a chronic disease, and it takes decades for the disease to evolve from its initial stages to the stage with clinical symptoms, there is a large window of opportunity for early intervention if susceptible subjects could be detected at early stage of disease. Although the advanced brain imaging techniques that were used in this thesis are still emerging and do not have clinical value yet, they have potential to serve as early imaging biomarkers for screening, early diagnosis and risk stratification.

Furthermore, cSVD is assumed to be part of a systemic disorder, which not only presents in the brain. The findings in this thesis support the development of faster, simpler and cheaper techniques for the assessment of microvascular function in peripheral more easily accessible organs as a proxy for cerebral microvascular function, even at early stages of the disease. Such surrogate biomarkers are probably more likely to be translated to widespread clinical practice for screening purposes than advanced brain MRI techniques. Examples include the use of retinal optical coherence tomography angiography, sublingual intravital microscopy, and blood biomarkers.

Next to early detection and prevention, there is an unmet need for effective disease modifying treatments. At the time, no effective treatments exist, except for treatment of established cardiovascular risk factors. A better understanding of the pathophysiology of cSVD is crucial in order to develop disease modifying treatments, and the knowledge acquired in this thesis can thus be used for the next step of real impact: the development of therapies. When effective therapies eventually become available, this would have a direct impact on patients, clinicians and society.

The systemic character of cSVD also implies that small vessel diseases can be clinically expressed in different organs within the same patient simultaneously. The most common other manifestations of systemic microvascular dysfunction include chronic kidney disease, retinopathy, and heart failure with preserved ejection fraction. These small vessel diseases all are highly prevalent, and have an undeniable socio-economic burden. This thesis contributed to the increasing knowledge on the systemic character of small vessel diseases and the shared pathophysiological processes underlying small vessel diseases in different organs. This renders opportunities for development of treatments that could benefit several organ systems simultaneously, which could lead to more cost-effective treatments and less polypharmacy, especially in older patients.

Communication of research findings

In order to reach impact, the content of this thesis must be spread among a scientific audience. This has been accomplished through the open-access publication of our results in several peer-reviewed journals. Study results were also presented at international conferences. Furthermore, as all research in this thesis was conducted as part of the EU Horizon 2020 financed CRUCIAL project, results have been shared with fellow researchers in consortium meetings, and all publications have been listed on the project's website (https://www.crucial-project.euhttps://crowdhelix.com/helixes/vascular/info). The consortium intends to organize a heart-brain symposium, which will render a great opportunity to share results with scientists with shared expertise and/or interest.

Conclusions

In several ways, this thesis contributes to a better understanding of the pathophysiology of cSVD, supports further optimisation and development of advanced brain MRI techniques, underlines the importance to acknowledge the multi-system character of cSVD, and gives directions for further research. Although there is no direct social or economic impact for society at this very moment, the gained knowledge contributes a piece to the puzzle and may eventually lead to the development of effective disease modifying treatments and methods to diagnose disease at an early subclinical stage. This may substantially reduce the socio-economic burden of dementia and stroke, as well as other small vessel diseases.

REFERENCES

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