

Cognitive function and cerebral small vessel disease in hypertension

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Valorisation

Introduction

Knowledge valorisation refers to “the process of creating value from knowledge, by making knowledge suitable and/or available for social and/or economic use, and by making knowledge suitable for translation into competitive products, services, processes and new commercial activities” (adapted definition based on the National Valorisation Committee 2011:8). In other words, it is the important translation of scientific knowledge to clinical or societal relevance.

Hypertension and the brain

Hypertension is a highly prevalent condition and is one of the leading risk factors for global disease burden. It causes damage in several end organs, such as the kidneys, heart and eyes. Guidelines recommend to routinely assess hypertensive organ damage in the heart and kidneys. Brain damage is less recognized as hypertensive end-organ damage and is an under-researched area, even though the brain is one of the main target organs affected by hypertension. It is known that hypertension-related brain damage is mostly due to cerebral small vessel disease (cSVD). As a consequence, hypertension is a major risk factor for cognitive deficits or dementia. This thesis contributes to raising the attention for these under-recognized consequences of hypertension and increasing our knowledge about influencing factors and predictors. As it is not possible to perform a neuropsychological assessment or brain imaging in every hypertensive patient, it is important to find predictors for lower cognitive function or brain damage in patients with hypertension to identify those patients at risk and in need of further investigation. It is important that these predictors are easy to apply in clinical practice.

Awareness for subjective cognitive failures in hypertensive patients

Patients complaining about cognitive problems may be a recognizable situation for clinicians. Most previous studies have shown that these subjective problems, also called subjective cognitive failures (SCF), have a strong association with poor physical health and depression. Although it might seem obvious that these SCF would also relate to objective cognitive problems, most previous studies did not find this relationship when correcting for mood and health. However, this relationship had not been examined in patients with hypertension, even though there is increasing support for an association between hypertension and objective cognitive impairment. We showed that in patients with hypertension, SCF are associated with objectively measured cognitive function and presence of cerebral microbleeds.

Our results have important implications for clinical practice. Clinicians working with hypertensive patients should ask for the presence of cognitive problems during consultation of patients with hypertension, as these SCF may point to lower cognitive function and brain

damage. It emphasizes the importance of performing a neuropsychological assessment and brain imaging when patients with hypertension report cognitive problems.

To increase awareness, it is important to inform both clinicians and patients. Therefore, in addition to a published scientific article, our results and the implications for clinical practice were described in the clinical implications section of *Hypertension*¹ and were commented on in an editorial commentary in the same issue.² In addition, a short summary of results was published on Dutch websites.³

The total SVD score

The different MRI markers of cSVD are generally investigated individually. However, in reality these markers might co-occur and it is thought that the occurrence of these markers together represents the severity of the underlying small vessel disease. Therefore, a “total SVD score” was recently proposed by our research group, which combines all individual MRI markers into one measure of SVD to capture total cSVD-related brain damage. This SVD score might provide a more complete overview of total SVD-related brain damage than just studying individual MRI markers.

In this thesis, we presented the first longitudinal study into the predictive value of the SVD score and we showed that the SVD score was associated with cognitive decline over 4 years. Our study contributes to the further validation and usefulness of the concept of a total score for cSVD. This total score uses visual rating of MRI and does not need computer software. This makes it an easy tool to use in clinical practice. Since the proposition of this total SVD score, interest has grown in such a total score and several other research groups have applied the score and showed that the SVD score is also associated with recurrent stroke and mortality. In addition, the concept of a total brain damage score has spread further. Other total scores have been proposed, such as a cerebrovascular disease burden score, which not only includes the presence of small vessel disease but also of large vessel disease, and a total MRI burden of SVD specifically adapted for patients with cerebral amyloid angiopathy. Further research should examine if the proposed SVD score could be improved, for example by increasing the range of the score. After further evaluation and research, the SVD score might be an easy way to detect patients at risk of future cognitive decline.

1 Clinical Implications. *Hypertension*. 2014;64:445-445.

2 Coca A, Sierra C. Beyond subjective cognitive failures in patients with hypertension? *Hypertension*. 2014;64:455-456.

3 <https://www.gezondheidsnet.nl/hersenen-en-geheugen/geheugenklachten-voorspellen-microbloedingen-in-de-hersenen>.

The role of hypertension in cSVD and cognition

Until now, only few studies had investigated longitudinal relationships between MRI markers of cSVD and cognitive function or cognitive decline. In this thesis, we showed that progression of periventricular white matter hyperintensities over 4 year is associated with cognitive decline in patients with hypertension. In addition, we reported that progression is more important in predicting cognitive decline than periventricular white matter hyperintensities already present at the start of the study. These results implicate that it is important to prevent progression of cSVD.

This thesis emphasizes the social and economic impact of hypertension-related brain damage and cognitive deficits and the high need of investigating the mechanisms of cSVD to consequently find prevention or treatment targets. The awareness of the research society is increasing and recently, the European Union's Horizon 2020 research and innovation programme funded the SVDs@target project. This project aims to elucidate the different mechanisms that are involved in microvascular dysfunction in cSVD. Maastricht University participates in this large European study. An important part of the study focuses on blood pressure and aims to unfold the pathways by which blood pressure affects SVD or cognitive function and identify novel therapeutic mechanisms that target the microvascular function of brain vessels.

In addition to studies focusing on the mechanisms of SVD or cognitive deficits, studies investigating the effect of antihypertensive medication on development or progression of cSVD or cognitive problems in patients with hypertension are needed. Existing randomized clinical trials did not give conclusive evidence about the effects of antihypertensive medications in this regard. Therefore, well-performed randomized controlled trials are needed to improve prevention of cognitive decline in patients with hypertension.

Conclusion

The results described in this thesis could help to (more easily) identify patients at high risk of lower cognitive function, future cognitive decline or cSVD-related brain damage. This provides information for clinicians to determine which patients are in need of further investigation, such as an extensive neuropsychological assessment or brain imaging. First, we showed the importance of awareness for subjective cognitive failures in patients with hypertension and the need of asking for cognitive problems during consultation of patients with hypertension. We spread these results in scientific and non-scientific ways to increase understanding in both patients and clinicians. Second, we showed that a recently proposed total SVD score could be useful in predicting cognitive decline. This score provides a more complete overview instead of studying individual MRI markers and can be easily applied in clinical practice. After further investigation this score could be used to identify

patients at high risk of cognitive decline. Third, we showed that progression of cSVD could result in a steeper cognitive decline in patients with hypertension. These results contribute to the increasing awareness of the role of blood pressure in cSVD and related cognitive problems. It emphasizes the importance of new studies in this field, such as the SVDs@target project, to find new ways to prevent cSVD progression and, consequently, cognitive deficits.