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Summary and conclusions
The general objective of this thesis was to study the causes and consequences of ventricular dilatation in aging. For this purpose, we used ventricular shape analysis to study potential new MRI markers of cognitive decline in aging, subjective memory complaints and AD. In addition, we designed a volumetric measure that may objectively quantify the disproportionate ventricular dilatation that is characteristic of NPH. We investigated the value of this measure for the selection of candidates with NPH for ventricular shunting, studied its association with NPH-like symptoms in the general population and used the measure to explore a possible cardiovascular origin of cerebral ventricular dilatation.

In chapter 2 a method of modeling and analyzing localized shape variations of ventricles was applied to a wide spectrum of cognitive levels. Each participant was assessed with the Mini-Mental State Examination (MMSE), yielding a study sample ranging from cognitively healthy to mild cognitive impairment, and from mild to advanced AD. The severity of periventricular atrophy was estimated as local enlargement of the ventricular surface relative to an average normal subject. We found that the severity of atrophy showed good correlation with MMSE score in the left thalamus, the left temporal horn, the left corona radiata, and the right caudate nucleus, increasing the number of potential biomarkers by means of ventricular shape analysis.

In chapter 3 the method of ventricular shape modeling was directed towards investigating possible local shape differences between cognitively healthy and persons with subjective memory complaints. In this explorative study, we found outward displacement of the ventricular surface adjacent to the thalamus and the corona radiata in persons with subjective memory complaints, compared with controls, suggesting that these structures may be involved in the development of subjective memory complaints. In addition, uncorrected results showed tentative evidence of local shape differences in the ventricular surface of the corpus callosum, hippocampus (inferior temporal horn), and amygdala (superior temporal horn).

Shunt surgery remains the standard treatment for NPH, despite high morbidity rates and lack of evidence indicating that shunt placement is effective in the management of this condition. Many diagnostic procedures have been described that may increase the probability of selecting the appropriate candidates for shunt surgery. In chapter 4 we studied the potential of volumetric assessment to distinguish between patients who respond to ventricular shunt surgery and those who do not. The preoperative ratio of ventricular volume and sulcal CSF volume was correlated with postoperative improvement in gait impairment, cognitive impairment, and bladder function. We found no difference in the mean preoperative ratio of ventricular volume and sulcal CSF
volume between subjects who improved on gait, cognition or bladder function and those who did not. This indicates that volumetric assessment has no predictive value in differentiating between NPH patients who will respond to shunt surgery and those who do not.

In chapter 5 we examined the association of disproportionate ventricular dilatation (expressed as the upper quartile of the ratio of ventricular volume and sulcal CSF volume) with gait impairment, cognitive impairment, and bladder dysfunction in a cohort of elderly persons from the general population. We found that those with disproportionate ventricular dilatation were more likely to have impaired gait and cognition. In addition, they were also more likely to have both impaired gait and impaired cognition. These associations were independent of white matter hyperintensity (WMH) volume. The presence of the radiological hallmark of NPH in persons with NPH triad symptoms in the general population raises the question whether more individuals could benefit from ventricular shunting.

Elaborating on earlier studies that suggested a vascular origin of disproportionate ventricular dilatation in NPH, in chapter 6 we hypothesized that ventricular volume out of proportion to sulcal CSF volume is caused by white matter atrophy resulting from small vessel disease. In order to quantify disproportionate ventricular dilatation, we used the ratio of ventricular volume and sulcal CSF volume (VV/SV) that was described in chapters 4 and 5. WMH volume was chosen to represent small vessel disease. We found that WMH volume was positively correlated with both ventricular volume and sulcal CSF volume. However, WMH volume showed a negative correlation with sulcal CSF volume. Our findings suggest that dilatation of the ventricles in patients with white matter hyperintensities is not a mere reflection of small vessel disease based atrophy, but that it may, at least partly, be based on active expansion of the ventricles. This unexpected finding sheds new light on the pathophysiology of NPH.

Future studies

Early detection

As our explorative study on ventricular shape differences in persons with subjective memory complaints discovered, anatomical differences compared to controls could be detected using ventricular shape analysis in the absence of objective changes in cognitive impairment. Further studies are necessary to investigate its possible value for the early detection of neurodegenerative disorders that are characterized by localized
or general cerebral atrophy, such as Frontotemporal Dementia and Parkinson’s Disease dementia.

Arterial stiffness
The theory of a vascular origin of NPH, which was supported by the findings of chapter 6, deserves further exploration with the inclusion of other parameters of arteriosclerosis and mechanical stress such as arterial stiffness. Studies of arterial stiffness in persons with disproportionate ventricular dilation could reinforce the hypothesis that propagation of pulsatile energy into the vascular bed of end organs such as the brain can lead to microvascular brain damage. Further knowledge of the relationship between arterial stiffness and disproportionate ventricular dilation could perhaps aid in the selection of candidates for shunt surgery.

Multimodality approach
The studies set out in this thesis are all based on post-processing of qualitative 1.5T based MRI images. Further possibilities for the study of intracranial CSF compartments lie in the field of higher field imaging (3T and up), as well as a combined approach using quantitative MRI techniques like brain perfusion imaging, phase-contrast cine MRI and MR elastography. In addition, data from neuroimaging studies combined with cerebrospinal fluid markers (amino acids, viscosity, pressure) or serum markers may lead to the discovery of new biomarkers of treatable NPH or the refinement of existing ones.

Longitudinal studies
The available literature on neuroimaging in Normal Pressure Hydrocephalus has until now focused on cross-sectional studies of ventricular dilatation, with the cause of dilatation being inferred from a number of features including the proportion between ventricular volume and sulcal CSF volume, as well as aqueductal stroke volume, the integrity of the periventricular white matter and the absence of a CSF flow obstruction. Longitudinal studies may be helpful in determining whether changes in the shape and size of the ventricular system occur due to (intermittently) elevated cerebrospinal fluid pressure or brain parenchyma loss leading to compensatory enlargement of CSF spaces.