The importance of vascular factors in the aging brain and dementia is increasingly being recognized. In this thesis we explored different vascular MRI measures, like total cerebral blood flow, large vessel disease and small vessel disease, in the clinical spectrum from normal aging to dementia, and we assessed relations between these MRI measures and several cardiovascular characteristics and risk factors. In addition, we aimed to get a better view of the clinical picture of dementia, determining the presence of neurological signs and neuropsychiatric symptoms in memory clinic patients and specifically in VaD, and additionally we assessed the relation between these signs and symptoms, and different MRI measures.

Summary

Cerebral blood flow in elderly

We examined the total blood flow to the brain in an elderly population in Iceland. Using 2D phase-contrast MR angiography, blood flow was measured in the basilar artery and the carotid arteries, and summed to calculate tCBF. In line with literature, increasing age was associated with a decrease in tCBF **(chapter 2.1)**.[1] Additionally, tCBF in elderly showed to be dependent on several different cardiovascular characteristics, including factors related to hematology, hemodynamics, and metabolic and cardiac disease. Moreover, some of these inverse associations with tCBF could already be found with cardiovascular characteristics assessed at mid-life, highlighting the importance to recognize cardiovascular disease early in life. Next to cardiovascular factors, it seems obvious that characteristics of the brain itself can influence blood flow due to a change of demand. TCBF is known to depend on brain volume, and with aging, brain volume decreases (i.e. due to processes such as neurodegeneration), while for example ischemic vascular lesions may progress.[2-4] We extended on previous cross-sectional studies on associations between brain volume and tCBF, by focussing in the next study on the relation between longitudinal measures of brain volume, including gray and white matter volume, WMH volume, and tCBF **(chapter 2.2)**. Relations were shown between higher annual grey matter and whole-brain atrophy and both lower tCBF and brain perfusion. Furthermore, annual progression of WMH was inversely associated with total brain perfusion, independent of age, sex and vascular risk factors. Collectively, the results suggest that brain tissue damage leads to a decreased demand for constituents of blood, implying a cycle of reduced demand and cerebral damage.

Vascular measures on MRI in mild cognitive impairment and dementia

Subsequent to aging of the general population as described above, we were interested cerebrovascular MRI changes in elderly with cognitive deficits. Although previous studies showed that both MTA and global cortical atrophy are independent predictors of progression to dementia in MCI patients, the impact of vascular disease on progression to dementia is less clear.[5-7] We examined patients with MCI and sought to determine the predictive value of cerebrovascular disease on MRI on progression to dementia **(chapter 3.1)**. Consecutive MCI patients of our outpatient memory clinic were included in the study and followed for 2 years. The presence of MTA and vascular disease (prescence of lacunes, microbleeds, infarcts, severity of WMH) was determined on baseline MRIs. In MCI patients, MTA and markers of cerebrovascular disease predicted progression to different types of dementia. MTA was a risk factor for progression from MCI to AD, while conversely the presence of cerebrovascular disease was independently associated with progression of MCI to a non-Alzheimer dementia, mostly VaD.
VaD has been reported to be the second most common type of dementia.[8] However, hardly any large studies in this patient group, e.g. on clinical or MRI characteristics, have been executed. To fill this gap of knowledge, we examined baseline characteristics of a large population VaD patients (n=706) included in a multi-center clinical trial on the effects of rivastigmine in VaD **(chapter 3.2)**. Based on MRI, patients were classified as having large vessel VaD, small vessel VaD, or a combination of both. We demonstrated that the diagnosis of VaD was in three-quarter of the patients based on small vessel disease, compared to just one fifth of the patients who fulfilled the criteria for large vessel VaD and one out of ten patients who fulfilled criteria for both types of VaD. Patients with small vessel disease were older and less educated, and showed more cortical atrophy and MTA than patients with large vessel disease. In contrast, patients with large vessel disease had more hypercholesterolemia and cardiac risk factors compared to patients with small vessel disease, illustrating heterogeneity between small vessel and large vessel VaD.

Neurological signs in dementia in relation to MRI measures

Next, we examined clinical features, other than cognition, in dementia, and sought to determine relations between clinical symptoms and MRI measures. To start with, we assessed the presence of extrapyramidal and unilateral signs in memory clinic patients, with AD, VaD, MCI and subjective complaints **(chapter 4.1)**. Furthermore, WMH volumes on MRI were extracted automatically with a method based on a Fuzzy interference system. We found extrapyramidal signs in 10% and unilateral signs in 12% of the patients. Adjusted for age and sex, extrapyramidal signs occurred more often in VaD compared to patients with subjective complaints. Unilateral signs were more prevalent in all groups compared to patients with subjective complaints. Moreover, we found that if unilateral signs were present, patients with subjective complaints and VaD showed more WMH, whereas there was no relation in AD and MCI.

Subsequently, we examined the presence of neurological signs more extensively in VaD **(chapter 4.2)**, determining the presence of a wide range of neurological signs in a large group of VaD patients and comparing the relative frequency of specific neurological signs dependent on type of cerebrovascular disease. Literature on this interesting topic is scarce, although presence of neurological signs is required according to current diagnostic criteria of VaD.[9] We found a median number of 4.5 signs per patient, with reflex asymmetry as most prevalent symptom. Measures of small vessel disease were associated with an increased prevalence of dysarthria, dysphagia, parkinsonian gait disorder, rigidity and hypokinesia and as well to hemimotor dysfunction. By contrast, in the presence of a cerebral infarct, aphasia, hemianopia, hemimotor dysfunction, hemisensory dysfunction, reflex asymmetry and hemiplegic gait disorder were more often observed.

Neuropsychiatric symptoms in Alzheimer's disease and vascular dementia

In the final part, we determined the prevalence of behavioural and psychological symptoms, first in AD **(chapter 5.1)** and second in VaD **(chapter 5.2)**. The prevalence of symptoms was high in both populations. Additionally, both in AD and VaD, apathy was the most prevalent symptom. In AD, we found no differences in prevalence of symptoms according to MTA or WMH, as rated on MRI, suggesting that the occurrence of symptoms in AD depends on other determinants, such as coping style or genetic make-up. Relations between specific distributions of WMH or atrophy and neuropsychiatric symptoms have also been suggested, as for example more sophisticated MRI measures found neuroanatomical correlates with the prevalence of symptoms in AD, such as apathy and grey matter density loss in the anterior cingulate and frontal cortex bilaterally.[10] Future studies are needed to confirm these hypotheses. In VaD, we found that patients with small vessel and large vessel VaD demonstrated different profiles of symptoms. Especially more apathy was reported in small vessel VaD and more agitation/agression in large vessel VaD, further underlining the heterogeneity between these two groups.

Discussion

Interest in vascular factors in relation to brain aging and dementia exists since long ago, for example as described by Alois Alzheimer who published several articles on 'mental disturbances' of vascular origin between 1895-1913.[11] Alzheimer was a respected neuropathologist (as well as neurologist and psychiatrist), and tried to link clinical features with vascular pathologies of the brain. Then, with the introduction of MR imaging in the mid-eighties, the research field changed enormously. Visualization of vascular abnormalities in the brain during life helps us to learn more about the origin of these changes and their clinical consequences. Due to the relatively novelty of the technique, MR imaging itself and methods to analyze imaging files underwent rapid developments and became more and more available, making examination of large populations possible.

Striking elements of this thesis are the investigation of several vascular MR measures like total cerebral blood flow, WMH and microbleeds. Furthermore, we examined the whole spectrum of normal aging to MCI and dementia, and explored both risk factors and clinical features. First, we showed relations between cardiovascular characteristics and longitudinal brain measures and tCBF in elderly.

Second, we demonstrated relations between vascular MRI measures and progression of MCI to dementia, and described different risk factor profiles for small vessel and large vessel VaD. Thirdly, we reported the prevalence of neurological signs and neuropsychiatric symptoms in memory clinic patients and specifically in VaD and determined relations between presence of signs and symptoms and different MRI measures. In our opinion, with these different aspects described in this thesis we contribute to the understanding of vascular changes on brain MRI and their clinical sequelae.

Methodological considerations

Selection of study population

A strong aspect of this thesis is the use of different research populations and study designs, including a population based cohort study, the study of memory clinic patients and analyses of baseline data of a large clinical trial. However, every study design has its own advantages and disadvantages. Strengths of population based studies, as applied in the first two studies of this thesis, are that besides survival bias, selection bias hardly plays a role. Furthermore, data are uniformly and prospectively collected. This allowed not only the examination of multiple cardiovascular characteristics of a large population, but additionally, with the combination of mid-life and late-life data, life course associations with tCBF could be examined. However, to gain more statistical power, for the study of diseases it is easier to examine cohorts of patients in a clinical setting. Patients visiting our outpatient memory clinic were studied to learn more about MCI and AD, and the presence of neurological signs was examined in the whole spectrum of patients with subjective complaints, MCI, AD and VaD. Prevalence of symptoms was compared between patients with subjective complaints and MCI or dementia. It must be noted that patients with subjective complaints have been shown to have a higher risk on progression to dementia compared to controls, and therefore might not be comparable to healthy aging.[12] VaD has been reported as second most prevalent type of dementia, however, the number of patients analyzed in our memory clinic was relatively small.[8] To be able to examine VaD patients more extensively, baseline data of a large multicenter clinical trial in VaD were examined, including one of the largest clinical series of patients affected by VaD to date. Nevertheless, the study design of a clinical trial may have had an effect on the inclusion of patients and perhaps has limited the possibility to generalize the results to the VaD patient group as a whole. Common to all three studies on VaD described in this thesis we found differences between patients with small vessel VaD and large vessel VaD, including differences in risk factor profiles, prevalence of neurological signs and severity of behavioural and psychological symptoms. Caution must be taken in interpretation of these results since all three studies covered the same study population, which might have had its influence on the consistency of the heterogeneity.

Diagnosis

The inevitable circularity of some studies might be a concern. In the study of MCI patients, it might not be surprising that patients with extensive vascular abnormalities on brain MRI are later diagnosed with VaD instead of AD. At baseline, none of the patients fulfilled the clinical criteria of dementia, and progression to dementia itself will not have been influenced by the MRI scan. Nonetheless, in assessing the different dementia types, MRI may have been used as a supportive element and therefore may have induced some circularity. Comparable circularity is conceivable for the study of neurological signs in VaD patients – that by definition are required to have neurological signs. However, we feel that the description of the relative frequency of a large number of neurological signs and their relations to specific types of imaged vascular damage, indeed adds to the field. Care should be taken though, that the NINDS-AIREN criteria, although generally considered accurate and specific, have been shown not to be interchangeable with other criteria for VaD.[13] Another potential limitation in the patient-related studies is misdiagnosis. Then again, all patients were carefully screened for fulfilment of current diagnostic criteria.

MRI techniques and assessments

Finally, different techniques were used to analyze the MR images. The technique we chose to measure cerebral blood flow has been shown to be non-invasive, fast and accurate.[14] On the other hand, it is a rather rough method to determine the total amount of blood flowing to the brain. To measure blood flow at brain tissue level, regional CBF per 100g brain tissue per minute can be assessed using

techniques such as positron emission tomography or dynamic contrast-enhanced MRI. However, these techniques are invasive and complex, and difficult to use in large study populations (- an exception may be arterial spin labelling [ASL], a novel MRI technique).[15]
Structural MRI measures were assessed sometimes visually, such as counting the number of lacunes or microbleeds or using visual rating scales, and sometimes we used fully-automatic volumetric methods for example to measure WMH volumes. Although an equal validity between visual ratings scales and volumetric methods has been reported, others suggested that volumetry is more sensitive to detect small group differences.[16, 17] Finally, we used operational definitions for the NINDS-AIREN criteria for VaD, which were carefully applied by central assessment. However, the radiological criteria to diagnose VaD are known to be complex, especially for inexperienced raters.[18] A low reliability in inexperienced raters has been described, and due to these problems with applicability, comparison of our findings to other studies may be difficult.

Clinical implications

Vascular risk factors

In our study on cardiovascular characteristics, we found associations between mid-life characteristics and tCBF at late-life. Accordingly, careful control of cardiovascular risk factors early in life to prevent cerebrovascular disease appears to be an important goal for clinical practice. Additionally, strong relations between late-life cardiovascular characteristics and late-life tCBF were shown, including characteristics related to hematology, hemodynamics and cardiac function. These results underline the significance to be aware of vascular determinants in the older population and keep them in optimal condition. Ultimately, vascular risk factors may lead to such low blood flow to the brain that ischemic small vessel disease or stroke will be the consequence. Additionally, risk factors such as high blood pressure and diabetes have been associated with brain atrophy on MRI.[19, 20] Moreover, vascular disease has been shown to increase the risk of both VaD and AD.[21] For example hypertension has been reported to triple the risk of VaD, in line with our finding in VaD patients, where hypertension appeared to be the most prevalent risk factor with a prevalence of 80% in the whole cohort.[21] In patients with dementia therapeutic options are relatively scarce, and risk factor related therapy in patients who already have dementia seems a logical step to prevent further vascular damage to the brain. Effects could also be expected in AD, as vascular factors were reported to be related to disease progression.[22, 23] Nonetheless, the role of cardiovascular medications in dementia has not been firmly established yet, and results can be confusing. The use of statins and beta-blockers has been reported to slow the rate of functional decline in AD.[24] In VaD patients, the use of antiplatelet or anticoagulant medication was related to a longer life expectancy than those without.[25, 26] On the contrary, AD patients using antiplatelet therapy had no benefit, but instead the use increased the risk of serious bleedings.[27] Furthermore, anticoagulant medication has been associated to a greater risk of intracerebral heamorrhages in the presence of microbleeds on MRI, which can be of high prevalence in dementia.[28] Future research to the effects of cardiovascular medication in dementia is needed.

Clinical features

Subsequent to the relation between cerebrovascular MRI measures and cardiovascular factors, we were interested in the relation between cerebrovascular measures and clinical features in dementia. Our results indicate that next to cognitive impairment, also neurological signs, such as extrapyramidal and unilateral signs, as well as behavioural and psychological symptoms are highly prevalent in dementia. In patients with dementia, both the presence of neurological signs and neuropsychiatric symptoms have been related to a worse prognosis, higher cost of care and earlier institutionalisation.[29-31] The high prevalence of symptoms in our studies highlight the importance to recognize these symptoms in clinical practice. In VaD, we found associations between WMH and other cerebrovascular disease, and the prevalence of neurological signs and neuropsychiatric symptoms, what seems to implicate that prevention of cerebrovascular damage may lead to prevention of these signs and symptoms. In AD it seems to be more complex. We did not find a relation in AD between severity of WMH and the prevalence of neurological signs or neuropsychiatric symptoms, suggesting that in AD these signs and symptoms depend on other characteristics. Future research is needed to unravel the structural underpinnings of both neurological signs and neuropsychiatric symptoms in AD.

Future perspectives

We examined cerebrovascular disease in the aging brain, using MRI to measure vascular changes. However, the research field is broad and there were several aspects we could not assess. For example more longitudinal research is needed to examine changes in cerebral blood flow overtime, to compare baseline and follow up blood flow and analyse intracerebral and clinical consequences of flow alterations. Furthermore, with the use of other techniques it is possible to examine brain perfusion; blood flow irrigating the brain expressed in milliliters per 100 gram of tissue per minute, corresponding to microcirculatory tissue perfusion rather than the flow of the main vascular axes. Techniques, like PET and dynamic susceptibility weighted MRI, are often complex and invasive, but hopefully will be available and applicable to large study populations one day. The same holds for novel MRI techniques, where for example diffusion tensor imaging has shown promising results to determine true white matter damage in cerebral small vessel disease, but availability of this technique needs to increase.[32]

Vascular measures

Although the radiological NINDS-AIREN criteria include important vascular disease such as infarcts, lacunes and WMH, some other measures are not incorporated. For example cortical microinfarcts seem also to contribute significantly to the progression of cognitive deficits in brain aging.[33] Additionally, microbleeds are not mentioned in the criteria, while in subcortical VaD the presence of microbleeds has been related to cognitive functioning.[34] Moreover, in our study in MCI patients, the baseline prevalence of microbleeds appeared to be higher in patients who progressed to a non-Alzheimer dementia (mostly VaD) than in patients who remained stable, which also seems to imply a relation between microbleeds and cognitive functioning. A fascinating fact regarding microbleeds is their relation to both to vascular disease and cerebral amyloid angiopathy. Cerebral amyoloid angiopathy is a cerebrovascular pathology which is found with an incidence of 80-98% in AD patients.[35] Therefore, microbleeds can potentially be regarded as the missing link between vascular disease and AD pathology. However, the origin of microbleeds in terms of risk factors and pathogenesis, as well as clinical consequences in both VaD and AD have to be elucidated in future research. Another issue include the radiological NINDS-AIREN criteria itself. The NINDS-AIREN criteria were designed in 1993, with recognition of the added value of neuroimaging.[9] At this moment, more than sixteen years later, the availability and the knowledge of brain imaging have remarkably improved. Now seems the time for a critical reappraisal of the criteria. For example involvement of at least 25% of the total white matter is considered sufficient for a diagnosis of VaD, but this percentage was set purely arbitrarily.[9] Moreover, application of this threshold is also debatable. Further work is needed to improve the quality of the radiological criteria for VaD and simultaneously increase their interobserver agreement.

Diagnosis of VaD

Proceeding with the above, the NINDS-AIREN criteria (which we used to diagnose VaD) are the diagnostic criteria that are currently most often used in VaD studies.[9] However, also other criteria such as the criteria of the International Statistical Classification of Diseases, tenth revision (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM IV) are in use. [31, 32] Since different criteria have been shown not to be interchangeable, comparison of different studies can be difficult.[13, 36, 37] In this day and age of globalisation, we plead for the application of only one and the same set of criteria, enabling everybody speak the same “clinical language”. In addition, we believe that, next to a reappraisal of the radiological criteria, further work is needed to refine the general criteria. We showed that cerebrovascular disease underlying VaD consisted in the majority of small vessel disease. Although small vessel disease is considered to develop gradually, the NINDS-AIREN criteria require a temporal relation between evidence of vascular disease and dementia.[9, 38] In our opinion, the temporal criterion can be omitted in the criteria for small vessel VaD. Furthermore, we demonstrated several differences in risk factor and clinical profiles between patients with small vessel VaD and large vessel VaD. The difference between these two types of VaD should at least be included in a more pronounced way in new VaD criteria. Finally, currently evidence of cerebrovascular disease includes next to imaging criteria the presence of neurological signs. However, with the widespread availability of imaging nowadays to establish the presence of vascular in a more direct way, it could be argued that the criterion of neurological signs should not be required.

VaD – AD

AD pathology and cerebrovascular disease are both very common, and as a result they inevitably occur together in many cases.[39] However, the association seems to be more complex than a mere coincidence, as there is now evidence for a significant AD – VaD overlap in terms of risk factors and clinical features. It has been suggested that AD and cerebrovascular disease may work synergistically to cause cognitive decline, but until now, it remains to be elucidated how the two interact. For example in the study of MCI patients, we found no predictive value of progression to AD of any of the vascular measures. On the other hand, in our sample VaD patients, moderate to severe MTA and cortical atrophy were shown, suggesting a relation between vascular disease and atrophy. Future research is needed to confirm our findings and further elucidate the interactions between vascular disease and AD pathology.

Clinical features

More research is necessary to the origin of clinical features in dementia. As earlier described, we did not find a relation between WMH and the presence of neurological signs or neuropsychiatric symptoms in AD patients. Possibly, in AD these signs and symptoms depend on other determinants, such as caregiver characteristics or genetic make-up. Additionally, it would be interesting to examine clinical features of AD in relation to more specific brain regions, looking at vascular disease, atrophy or regional cerebral blood flow. Recently, with the use of voxel-based-morphometry, certain foci of grey matter loss have been related to different neuropsychiatric symptoms.[10] Future studies of this kind may help to clarify the mechanisms and brain circuits involved in certain clinical features in dementia.

In conclusion, we hope that this thesis will result in further study on the significance of vascular disease in aging and dementia, emphasizing the combination of state of art novel brain imaging techniques with rigorous clinical evaluation and etiological and treatment studies.

Conclusions

The following conclusions can be drawn from the studies presented in this thesis:

1. Total blood flow to the brain in elderly is dependent on several cardiovascular characteristics of which hemoglobin and hematocrit levels, diastolic blood pressure and cardiac disease are the most important. Additionally the associations with tCBF can be traced back to cardiovascular characteristics at mid-life.

2. Longitudinal MRI measures, as whole-brain and grey matter atrophy, and progression of WMH per year, predict total blood flow to the brain in elderly.

3. In patients with MCI, MTA and markers of cerebrovascular disease predict progression to different types of dementia. MTA is a risk factor for progression from MCI to AD, while conversely the presence of cerebrovascular disease is associated with progression of MCI to a non-Alzheimer dementia, mostly VaD.

4. Cerebrovascular disease underlying VaD consists in the majority of small vessel disease and in about one fifth of large vessel disease. Heterogeneity exist between these two groups with regard to risk factor profile and atrophy scores on MRI, the severity of the atrophy being higher in patients with small vessel disease compared to patients with large vessel disease. In contrast, patients with large vessel disease have more cardiac risk factors compared to patients with small vessel disease.

5. Neurological signs are common in a memory clinic population, but are only modestly related to WMH.

6. In VaD patients, specific neurological signs differ according to type of imaged cerebrovascular disease, with small vessel disease being often seen with more subtle signs, including extrapyramidal signs, whereas large vessel disease is more often related to lateralized sensorimotor changes and aphasia.

7. Behavioural and psychological symptoms have a high prevalence among AD patients, but there is no difference in prevalence of these symptoms according to MTA or WMH as rated on MRI.

8. In VaD, behavioural and psychological symptoms are commonly reported. Small vessel VaD and large vessel VaD show different profiles of symptoms, with especially more apathy in small vessel VaD and more agitation/aggression and euphoria in large vessel VaD.

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