Changes in total cerebral blood flow and morphology in aging

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Chapter 1

Introduction

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Aging is an inevitable biologic process that starts at birth[1] and continues irreversibly till death. Contrary to the general belief, physiologic aging does not always imply a diminishing intellectual functioning[1,2]. Cognitive decline is a sign of pathologic aging, and it is most often caused by ischemia in the brain[1].

Several age-related changes in the brain have been reported. In the elderly, white matter hyperintensities (WMH) are the most striking changes in the brain that can be perceived on conventional magnetic resonance imaging (MRI). WMH are defined as areas of high signal intensity in the white matter on T_2 weighted MRI sequences. The prevalence in healthy subjects over 60 years of age is 30% and this prevalence is rising with age[3]. Known risk factors for WMH are: age, female sex[4], aortic atheroslcerosis[5], and elevated systolic blood pressure[6]. These risk factors corroborate the view that vascular factors lead to hypoperfusion and ischemia, which eventually cause WMH[3]. There is no direct relationship between WMH and cognitive functioning in the elderly. In some studies a correlation is observed between WMH and cognitive functioning[7,8] whereas in other studies no such relationship is found[9,10]. These data suggest at least that other factors also influence cognitive functioning in the elderly.

Another finding that is frequently observed on imaging studies of the brain in the elderly is atrophy. Pathology studies have shown that after the age of 50 years the loss of brain weight amounts to approximately 2-3% per decade over the next four decades[11]. The presence of atrophy has been shown to be independent of the occurrence of WMH[12]. Very little is known about risk factors for global cerebral atrophy. It is generally thought to be caused by loss of neurons[11,13]. In subjects with dementia greater amounts of atrophy are seen[11].

Other changes seen on conventional MRI are hypointensities on T_2 weighted images in the caudate nucleus and putamen during aging[13]. These hypointensities are caused by an increase in iron content. Because of this high iron concentration these structures are susceptible to oxidative injury. This could explain the decline in mobility that occurs with normal aging[13].

Apart from the age-related changes that can be observed using conventional MRI techniques, additional changes can be detected in the elderly using quantitative MRI techniques. Diffusion weighted imaging showed a decrease in relative anisotropy with increasing age, without changes on conventional MR images[14]. Using Magnetization transfer imaging (MTI), a quantitative MRI technique, differences were found in normal appearing white matter (NAWM) between elderly and young subjects[15]. The causes and consequences of these age-related changes in normal appearing brain tissue have not been

unravelled yet. Bronge et al. demonstrated that these changes could be attributed to subtle histological changes characterized by less myelin staining but with a preserved axonal network and glial cell density[16]. Rovaris et al found a correlation between diffusion parameters, MTR parameters and atrophy, suggesting these lesions have a similar origin[17].

Several factors could be responsible for the poor correlation that is generally observed between age related changes in the brain and changes in cognitive functioning in the elderly. First, in most studies the lesion load in cerebral white matter is quantified by assessing the volume of WMH. However, there are indications that WMH, despite their similar appearance on conventional MRI, are diverse and represent lesions with very different stages of tissue damage. Second, in most studies correlating structural brain changes and cognition, changes in normal appearing brain tissue are left out of the equation.

Whatever the exact relationship between structural brain changes on MRI in the elderly and cognitive decline, cardiovascular risk factors have shown to cause considerable cognitive impairment in the elderly[8]. This relation suggests that changes in cerebral perfusion play an important role in the development of age-related cognitive loss. Under normal conditions, perfusion of the brain is kept constant over a wide range of systemic blood pressures. Known compensation mechanisms for a decrease in cerebral perfusion are a reduction of cerebrovascular resistance, recruitment of collateral vasculature, and increase of oxygen extraction[18]. When these compensation mechanisms are no longer sufficient to maintain adequate perfusion pressure of the brain, ischemia can be the result. Ischemia induced cerebral tissue changes can be a cause of functional loss. The ability to keep the brain perfusion within certain limits is called cerebrovascular reserve capacity (CVR). The coupling between O_2 supply and cerebral vascular tone remains to be elucidated. Presently, it is unknown whether changes in CVR play a role in the development of cognitive impairment in the elderly.

Aims of this thesis

1. To assess reproducibility of new methods for measuring total cerebral blood flow and cerebrovascular reserve capacity.

2. To assess whether aging affects total cerebral blood flow and cerebrovascular reserve capacity.

3. To assess whether the cerebrovascular reserve capacity in the elderly can be pharmacologically affected.

4. To assess whether WMH and changes in normal appearing brain tissue are manifestations of the same underlying pathogenesis.

5. To assess whether, using MTI, differences can be detected in various categories of WMH.

6. To assess the functional relevance of WMH, atrophy, MTI measures of cerebral lesion load (including changes in NAWM), and total cerebral blood flow in normal aging and dementia.

Outline of this thesis

First, in chapter two, we assessed the reliability, long term, and short term reproducibility of measurements of total cerebral blood flow using phase contrast MRI. In chapter three an automated method for assessing blood flow velocity profiles in phase contrast MRI is provided and validated. In chapter four we introduce two methods for measuring the cerebrovascular reserve capacity and compare these methods. In chapter five we assessed the involvement of NO in the CVR mechanism. In chapter six we tried to answer whether the cerebrovascular reserve capacity is diminished in the elderly.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary small vessel disease. CADASIL is often perceived as a monogenetic model for vascular dementia. Our methods for measuring total cerebral blood flow and cerebrovascular reserve capacity were used in CADASIL patients in chapter seven to explore the relation of flow disturbance and WMH in patients with CADASIL.

In chapter eight we studied the relationship between age-related WMH and MTR changes in the brain to see if these two findings are different manifestations of the same underlying pathology or whether they reflect different neurodegenerative processes. Different types of WMH were studied with MTI in chapter nine to assess whether the differences that are known to occur in WMH from histological studies can also be identified with quantitative MRI sequences.

In the last study we studied indicators of structural brain damage and flow in two groups of elderly. One group consisted of elderly subjects with very good cognition and the other group comprised subjects with dementia. The results of this study are shown in chapter ten.