Neurodegeneration and microvascular dysfunction

Chapter 11.2 Impact paragraph

Impact paragraph

In the impact paragraph we discuss the novelty of the findings of this thesis as well as the potential clinical, societal, and scientific impact of the findings of this thesis. The impact paragraph is composed as follows. First, we provide background information on the topic; second, we provide a brief summary of the main findings of this thesis; third, we discuss the novelty of the findings of this thesis; and fourth we, consecutively, discuss the potential clinical, societal, and scientific impact of the findings of this thesis.

Background

There is an imperative for the early prevention of major clinical disease of a neuronal and microvascular origin such as dementia,[1] late-life depression,[2] and diabetic retinopathy.[3] Importantly, these diseases can have debilitating effects on the quality of life of patients and their family; are associated with a high societal burden in terms of health costs; and an epidemic increase in the number of patients with these diseases is expected in the next 25 years.[1-4] Prevention of the above major clinical diseases may be possible via prevention of neurodegeneration and microvascular dysfunction, which precede symptoms of these major clinical diseases. However, the existing literature on the causes and consequences of neurodegeneration and microvascular dysfunction has important knowledge gaps.[5,6]

In view of the above, we in this thesis investigated 1) whether potentially modifiable cardiovascular and lifestyle factors are determinants of neurodegeneration and microvascular dysfunction; and 2) how neurodegeneration and microvascular dysfunction are associated with (early-stage) symptoms of major clinical disease, including more (clinically relevant) depressive symptoms and lower cognitive performance. In this thesis neurodegeneration was assessed in the retina; and microvascular dysfunction was estimated from indices of microvascular dysfunction assessed in the brain, retina, skin, kidney, and blood.

Main findings

Main findings of the present thesis are that potentially modifiable cardiovascular and lifestyle factors may be determinants of neurodegeneration and microvascular dysfunction; and that neurodegeneration and microvascular dysfunction are associated with, and/or precede, symptoms of major clinical disease (i.e. [clinically relevant] depressive symptoms and lower cognitive performance). Importantly, of the potentially modifiable cardiovascular and lifestyle factors under study, type 2 diabetes was the strongest determinant; and in individuals with, versus without type 2 diabetes certain

determinants under study (e.g. hypertension and arterial stiffness) were more strongly associated with neurodegeneration or microvascular dysfunction.

Novelty of concepts under study in this thesis

The concept of preventing major clinical disease of a neuronal and microvascular origin via early-stage modification of cardiovascular risk factors and adverse lifestyle factors is not novel. Alternatively, the following concepts, i.e. potential implications of the findings of this thesis, are relatively novel: 1) (retinal) indices of neurodegeneration and microvascular dysfunction may be biomarkers for the early-stage identification of individuals at risk for major clinical disease; and 2) (retinal) indices of neurodegeneration and microvascular dysfunction may be biomarkers for the monitoring of early-stage (subclinical) disease progression.

Potential clinical impact

We address two main clinical implications of our findings. First, findings of this thesis support the concept that there may be an opportunity to prevent and/or slow the onset of major clinical disease of neuronal and microvascular origin via the early-stage prevention of exposure to cardiovascular risk factors and adverse lifestyle factors. Possibly, implementation of therapeutic strategies that aim to prevent exposure to these factors may result in a reduction in neurodegeneration and microvascular dysfunction, and, consequently, to a reduction in the number of patients that develop major clinical disease. Second, findings of this thesis are in support of the concept that (the investigated) indices of neurodegeneration and microvascular dysfunction may be biomarkers for the early-stage identification of individuals at risk for major clinical disease; and that (the investigated) indices of neurodegeneration and microvascular dysfunction may be biomarkers for the early-stage monitoring of (subclinical) disease. Hence, potentially in a near future, there may be an opportunity to prevent major clinical disease in a more personalized and targeted (thus better) manner than currently possible.

Potential societal impact

If findings of this thesis are translated in to clinical practice the societal impact may be large.

Better prevention of major clinical disease may increase the health of a large number of individuals in the (near and late) future as a large number of individuals are at risk for dementia, late-life depression, and diabetic retinopathy. Epidemiologically, up to 1/3 and 1/7 women and men, respectively, are expected to develop dementia in their

lifetime[7] (in the Netherlands in 2021 currently N=290,000 individuals suffer from dementia); up to 1/9 individuals is at risk for a lifetime episode of depressive symptoms;[8] and up to 1/2 individuals with diabetes, currently approximately 1 million individuals in The Netherlands, is expected to develop some sign of diabetic retinopathy during their life time (i.e. ~500,000 individuals).[3] Additionally, as individuals with type 2 diabetes have an increased risk of developing dementia and late-life depression and the number of individuals with type 2 diabetes is expected to strongly increase in the upcoming 25 years, specific targeted prevention in individuals with type 2 diabetes may (considerably) contribute to the prevention of major clinical disease.[1-4]

Any reduction in the speed of the onset of major clinical disease, and/or any prevention of dementia, late-life depression, and diabetic retinopathy may have an important impact on the burden of major clinical diseases, both at the level of an individual (i.e. impacting the quality of life of patients and their family and friends) and at the level of the society. An example of the impact on the personal and societal burden is that prevention and/or slowing of the onset of diabetic retinopathy may prevent and/or reduce the number of life years with visual impairment and blindness (which can, at the level of an individual, improve quality of life; and, at a societal level, can reduce the loss of productive years of professional labour).[3] A second example of the impact on the societal burden is that prevention of major clinical disease may relevantly reduce the financial burden of these diseases on the national health budget (as health costs due to major clinical disease can be very high; e.g. as nearly 10% of the annual healthcare budget of the Netherlands is spent on healthcare for individuals with dementia, reducing the number of individuals that develops dementia may importantly reduce the financial burden of dementia on the healthcare budget of The Netherlands).[9]

Scientific impact

Findings of this thesis may have certain implications for future clinical research.

Here we discuss three main implications (a more detailed overview of implications for future research is presented in the general summary and discussion section [Chapter 10]).

First, in order to enable moving from a research setting to clinical practice, future researchers should aim to further confirm findings of this thesis in cohort studies with longitudinal data available; and (in a later stage) quantify the impact of early modification of cardiovascular risk factors and lifestyle factors on neurodegeneration and microvascular dysfunction in randomized controlled trials. We discuss two examples of such trials that could be conducted. A first example is that future researchers may investigate in clinical trials whether early monitoring and treatment of

daily glycaemic variability, blood pressure variability, and arterial stiffness can result in a clinically relevant reduction of neurodegeneration and microvascular dysfunction (on top of therapies which are currently used in clinical practice). A second example is that future researchers may aim to develop and evaluate type 2 diabetes-specific strategies to prevent neurodegeneration and microvascular dysfunction.[10,11]

Second, future researchers should further investigate how retinal and brain neuronal and microvascular (patho)biology relate to each other and perform research which aims to move retinal biomarkers from a preclinical research setting to a clinical setting. To start, future aetiological research may provide (cellular) population-based insight in the early pathobiology of brain disease (e.g. by using novel imaging techniques such as adaptive optics to image neurodegeneration at a cellular level in the retina).[12] Then, research with a clinical focus may seek to quantify the diagnostic potential of retinal indices of neurodegeneration and microvascular dysfunction (e.g. by investigating the clinical diagnostic value of these tools in a memory clinic setting). Next, in order to enable monitoring of neurodegeneration and microvascular dysfunction in the clinic, researchers should perform research that aims to obtain reference values for change in retinal neuronal and microvascular structures over time.[13]

Third, this thesis demonstrates that combining multiple (medical) disciplines, which are traditionally separated from each other, is a promising strategy for future research. In this thesis the disciplines ophthalmology, neurology/psychiatry, and internal medicine were combined. Therefore, future researchers may consider to pursue collaborations in multidisciplinary research teams.

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