Biomarkers of Alzheimer's Disease

Knowledge valorization

The knowledge resulting from the studies described in this thesis is not only of value to the scientific community but also has clinical and societal relevance. This paragraph addresses the importance of our studies and potential implementation opportunities in- and outside the academic setting.

Relevance

Dementia is a devastating disease which affects approximately 50 million people worldwide, a number that is expected to triple by 2050 due to the aging population. Alzheimer's disease (AD) is the most common form of dementia as it accounts for 60-80 percent of dementia cases. The disease places a heavy burden on patients, family and caregivers and due to the increasing prevalence, it has also become a major challenge for societies, economies and healthcare systems. In 2015, the global costs of dementia were estimated around 818 billion US dollars and this year, 2018, they are expected to cross the threshold of 1 trillion US dollars. Dementia is a problem that requires worldwide attention. This vision is supported by the Global Action Plan on the Public Health Response to Dementia of the World Health Organization (WHO) which stimulates governments to facilitate scientific research and optimize care for patients.

In current clinical practice, no disease modifying treatment for AD can be offered. Thus far, results from clinical trials examining potential drugs have been disappointing. A reason for this could be that the therapeutics are offered too late in the disease process when damage to the brain has become irreversible. Therefore, many studies now aim to identify individuals before they have AD-type dementia in order to start interventions earlier. This thesis has also contributed to this effort as we created novel normative data based only on individuals without amyloid-β (Aβ) which are more sensitive in identifying individuals at risk of developing dementia. On the other hand, the studies in this thesis underline the multifactorial nature of AD and thereby stress the importance of multifactorial secondary prevention. We showed that although vascular risk factors and vascular pathology do not have a direct effect on Aβ, they do have an effect on neurodegeneration and thereby possibly also on the rate of cognitive deterioration. In addition, our results suggest that processes like axonal degeneration, synaptic dysfunction and astroglial activation play a role already very early in AD and may have a profound effect on cognitive decline, making them potential targets for disease modifying treatments. Moreover, the studies in this thesis improve prognostic accuracy for current and future patients which can be extremely

valuable for patients, caregivers and family members as well as for healthcare institutions and policymakers.

Targeted audience

The studies described in this thesis may be of relevance to a broad audience. First, our results are relevant for clinicians responsible for assessing and diagnosing individuals with cognitive problems. Our results may aid with the interpretation of biomarker and neuropsychological reports and improve prognostic accuracy. As clinicians could use our results to provide a more accurate prognosis for patients in various stages of the disease, our results are also, indirectly, relevant for patients and caregivers. Next, our results are also highly relevant for scientists as they increase understanding of AD pathophysiology and improve diagnostic and prognostic accuracy and provide a basis for future prevention studies. In addition, the data sharing infrastructure built as a methodological basis for the studies in this thesis is a powerful and valuable tool for future studies in the field of AD but also other disease areas. Fourth, our studies could be of relevance to pharmaceutical companies as they provide insight into mechanisms underlying AD which help to identify novel treatment targets, to select participants for trials and to identify outcome measures for clinical trials. Lastly, this thesis may also be of interest to policy makers as our studies underline the importance of research into AD as this increases the knowledge that is needed to find effective treatments for AD. For policy makers, it is also interesting to learn that a promising prevention strategy for AD may be to treat vascular factors which have shown to be associated with AD pathology.

Products

The infrastructure built as part of the European Medical Information Framework for AD (EMIF-AD) facilitates reuse and combining of existing data and is a product of the studies conducted in this thesis. The facilities created as part of EMIF-AD – the online catalogue, data platform and the AD-Switchbox - are sustainable and can be utilized by researchers worldwide and could also be adapted to facilitate research in other disease areas. A special product resulting from EMIF-AD is the EMIF-AD Multimodal Biomarker Discovery (MBD) cohort. Because of its sample size and unique multimodal data collection, this cohort will be instrumental to study the early pathophysiology of AD in detail. Lastly, the normative data based on individuals without Aβ will be valuable for clinical practice, research and for pharmaceutical companies as it increases the diagnostic accuracy of early AD.

Innovation

The studies described in this thesis were aimed to unravel several pathological mechanisms underlying AD beyond the involvement of the classic AD pathology in large sized studies. This provides a novel, multifactorial view of the disease and shows the involvement of different mechanisms along the course of the disease. Moreover, we studied new concepts such as atypical biomarker profiles (e.g. Suspected Non-Alzheimer's disease Pathophysiology, SNAP) and novel diagnostic and prognostic biomarkers. The methodological background of this thesis is unique as we used large datasets only by reusing and combining existing data. The data sharing infrastructure may set the standard for worldwide collaborations aimed to tackle major healthcare challenges such as finding effective treatment for AD. In addition, we were among the first to study the influence of vascular risk factors on longitudinal cerebrospinal fluid (CSF) biomarkers, which provided support for possible causal relationships.

Implementation

The data sharing infrastructure developed as part of this thesis is already being used by a large number of researchers around the world and we have secured funding to sustain this infrastructure in the near future. Our results regarding vascular contributions to AD are now part of the scientific literature which can be used to shape prevention studies and trials for AD. In addition, in the Discussion chapter of this thesis we provided future directions regarding software that could aid to bridge the gap between research findings. The proposed software for clinicians which facilities storage and interpretation of elaborate patient profiles with respect to biomarkers, neuropsychological data and co-morbid disorders can be developed in a future scientific project.