The Path of Alzheimer's disease

KNOWLEDGE VALORIZATION

This paragraph addresses the significance and impact of the studies described in this thesis by outlining how knowledge resulting from our studies can be made valuable for clinical and social use.

Societal relevance

With about 40 million people worldwide having dementia and the expectation that this number will double in the next 20 years due to the aging population, dementia may be the greatest health-care challenge of our time. AD is the leading cause of dementia, contributing to about 70% of cases. At present, no cure or disease-modifying treatment is available for AD. The progressive nature of AD posits a huge burden on the ones affected, their families and caregivers. The increasing prevalence also poses a major challenge for the wider society and health care systems and has great economical impact. In 2010 the global cost of dementia was estimated at 600 billion US dollars, increasing to 818 billion in 2015. This impact threatens to increase as well because more people live into old age. For these reasons, the World Health Organization (WHO) and the European Union (EU) have indicated that dementia should be regarded as a global public health priority. For governments, this results in a need to provide more resources to search for AD therapeutics and to arrange care for patients.

Future AD therapeutics are most likely to be effective in the earliest stages of the disease, when neuronal damage is still limited. A major challenge in the development of effective treatment for AD therefore is the early identification of people at risk for AD-type dementia. Studies in this thesis aid in the identification of individuals in an early stage of disease who are most likely to benefit from treatment. This makes it possible to target new treatments at the right population resulting in reduced costs associated with trial screening. When effective treatment for AD becomes available, early identification of AD is still important since the cost-effectiveness of treatment will eventually depend on the strategy for identification of patients eligible for that treatment.

Furthermore, studies in this thesis promote an early and accurate diagnosis in people with cognitive complaints. An accurate and timely diagnosis is a prerequisite for access to appropriate support services and symptomatic treatment, which will likely reduce health care costs. Accurate diagnosis and prognosis are also important for patients and caregivers to end uncertainty associated with cognitive complaints and it allows them to make arrangements for the future. Differential diagnosis of the cause of dementia can be important for treatment decisions and for making an individualized prognosis. Findings in this thesis provide guidelines for the use of biomarker assessment and neuropsychological assessment in current clinical practice.

Target audience

The findings described in this thesis are relevant for current and future patients and caregivers, clinicians, researchers, pharmaceutical companies, research organizations and policy makers.

Our results are relevant for people with cognitive complaints who want to know their diagnosis and prognosis, and for clinicians responsible for making this diagnosis. The results of this thesis will aid in improving the accuracy of diagnosis and prognosis by increasing knowledge about biomarker assessment and interpretation of biomarker results and about early neuropsychological indicators of incipient AD. As a result, clinicians can better inform patients and their families about their prognosis and what specific actions could be taken.

Also, products resulting from this thesis are relevant for researchers in the AD field. The infrastructure as well as the database resulting from the collaboration we initiated can be utilized as a valuable resource for researchers. Researchers can employ the prevalence estimates generated in our studies as starting point for analyses or to select participants for their studies.

Pharmaceutical companies started using biomarker-based inclusion criteria to only select amyloid positive participants for clinical trials to ensure that participants can benefit from anti-amyloid therapy. However, this is costly because it results in many screen failures since only a subset of persons without dementia have amyloid abnormalities. Clinical trial screening costs in the US are approximately 7500 US dollar (amyloid-PET scan, MRI, clinical and cognitive testing, laboratory measures) per participant. Studies in this thesis are highly relevant for prescreening and can help to reduce screening costs of pharmaceutical companies. Also, our findings can be used to optimize clinical trial design by assisting in defining clinical end-points and determining which factors need to be considered when evaluating the effect of interventions.

In view of the rapidly increasing costs of dementia with little progress in developing an effective treatment so far, an increase in investment by research organizations in the search for effective pharmacological and psychosocial AD therapeutics is needed. In order to identify windows of opportunity for intervention, studies need to start in midlife, have a long duration and assess the disease from a multidisciplinary view. Studies in this thesis provide insight in the pre-dementia phase of AD and its heterogeneity in onset and progression, underscoring the need to invest in long-term research to eventually reduce the burden for patients and society. For now, policy makers involved in health care regulations could use the results of this thesis to adapt their recommendations about neuropsychological and biomarker assessment in diagnostics concerning cognitive symptoms.

Products

Based on the studies in this thesis, a tool for prescreening of persons with an increased risk for amyloid positivity was developed. A major obstacle for AD clinical trials is the high cost and time required to screen large numbers of candidate participants to meet specific trial inclusion criteria. Amyloid imaging and CSF biomarkers enable early detection of AD and can therefore identify who has a high risk of progression to AD-type dementia. Predicting amyloid positivity

can be improved in a noninvasive an inexpensive way by using the prevalence estimates generated in our studies as screening tool. In our future studies, we will improve this screening tool to promote the generation of more individualized risk profiles such that the tool can also be implemented in clinical practice.

Another product resulting from this thesis is the large harmonized database including data from over 10,000 participants who underwent amyloid biomarker assessment at 56 research sites from across the world. Researchers can make use of the infrastructure resulting from this multicenter study upon request and the database can ultimately be utilized as resource for researchers in the AD field. This data sharing initiative is ongoing and open to new contributors.

Innovation

Studies in this thesis advance the characterization and identification of persons at risk for AD and hence our conception of the development of AD. The pre-dementia phase of AD was examined from biomarker, neuropathologic and clinical viewpoints in this thesis, providing the possibility to integrate findings at different levels. Further, we included participants with all diagnoses across the cognitive spectrum. In this thesis, the first multicenter study using data from a total of 56 studies to predict amyloid positivity was described. Formation of large international collaborations is needed to accelerate progress in AD research. These studies also set an example of data sharing and openness to avoid redundant research in the field.

Implementation

Findings on the use of biomarker and neuropsychological assessment resulting from this thesis can be translated into clinical practice through incorporation in clinical guidelines. To assure generalization to all hospital and memory clinics, recommendations also require validation by other research groups.

The prevalence estimates generated from our studies have already been disseminated to the public through publication in scientific journals, presentations at international meetings, news websites and social media and are being implemented in the screening process of pharmaceutical trials. Ultimately, the screening tool can become available for clinicians to use in daily clinical practice to make an accurate prediction on individual patient level. However, the relationships between amyloid positivity and demographic, comorbid and lifestyle factors and other biomarkers for AD first need to be investigated more closely. Knowledge on the rate of decline in subjects with amyloid pathology and on factors affecting the relation between amyloid pathology and cognitive decline should also be increased to aid the development and implementation of individualized screening and therapy. If the tool is ready to be used for individual predictions, there will still be risks associated with implementation in clinical practice. Clear information about advantages and disadvantages of the tool and its outcomes should therefore be available before implementation.