Cognitive correlates of cerebrospinal fluid biomarkers for Alzheimer's disease

KNOWLEDGE VALORIZATION

The overall aim of our studies was to aid in the early identification of AD before the onset of dementia and to obtain a better understanding of the pathophysiological mechanism of AD and predictors of disease expression in order to facilitate treatment development. In addition, early identification of AD and a better understanding of clinical disease progression will benefit present patient care by allowing for timely psychosocial interventions and to assist patients and caregivers in an early stage. For this purpose, we examined associations between established and emerging biomarkers and risk factors for AD, and cognitive decline across the clinical spectrum of AD ranging from preclinical AD to mild dementia. This chapter addresses the clinical and societal relevance and implications of our studies.

Societal relevance

Dementia may be one of the greatest global health challenges of our time due to its impact, size and costs. With the aging of the population, the number of individuals with dementia has increased up to approximately 50 million in 2017 worldwide, and is expected that it will double every 20 years. AD is the most common form of dementia and contributes to 60-70% of cases with dementia. Dementia is the seventh leading cause of death and places a huge burden on patients and caregivers. The increasing prevalence imposes an enormous challenge for society and the health care system. Worldwide the costs for dementia have been estimated as $818 billion in 2015, which increased by 35% since 2010. The World Health Organization (WHO) considers dementia as a public health priority and recommends every country to develop a national dementia plan and a framework for action. More resources are needed to facilitate treatments studies, care for patients and prevention studies.

At present no disease modifying treatment for AD exists. Future disease modifying treatments are most effective when neuronal damage is still limited before the onset of dementia. Still it is challenging to find individuals without dementia with AD. Studies in this thesis may aid in the early identification of non-demented individuals without dementia with underlying amyloid or tau pathology. This can be valuable for prescreening of the population for treatment studies such that these trials can recruit participants faster and at lower costs. This may ultimately benefit patient care. Our results showed that early episodic memory dysfunction is a sensitive cognitive marker for early AD pathology, although the diagnostic accuracy was modest. In addition, we provided further evidence for the role of complement dysfunction in early AD pathophysiology, which may also guide future treatment development.

Studies in this thesis may also benefit present patient care by aiding in our understanding of predictors of clinical disease progression. We tested the association between established and emerging AD biomarkers and cognition over time. We demonstrated that in particular tau, but also odour dysfunction may be useful as marker for predicting future cognitive decline. We also tested the association between modifiable lifestyle factors and AD biomarkers and conversion to AD-type dementia in individuals without dementia with cognitive complaints. Previous studies showed that lifestyle risk factors increase the risk for dementia. We did not find an association between modifiable lifestyle factors and AD biomarkers or conversion to AD-type dementia in individuals without dementia with cognitive complaints. This suggests that targeting lifestyle may have limiting effect on AD pathology or conversion to AD-type dementia in individuals with cognitive complaints, and that these lifestyle risk factors likely impact dementia through non-AD related pathways. This information can be valuable for future dementia prevention programs.

Target audience

The findings described in this thesis are relevant for clinicians by increasing knowledge of utility of established and emerged AD markers for diagnosis and prognosis, and the utility of risk factors for predicting disease progression. In turn, this will aid in our ability to inform patients and caregivers in the future about the underlying etiology of the clinical diagnosis and future cognitive decline, which can benefit patient care.

Our findings on pathophysiological mechanism of AD, clinical disease expression, and risk factors may be relevant for researchers for planning future studies such as prevention trials aimed at modifying pathophysiological processes and studies targeting modifiable lifestyle factors to prevent dementia and AD pathology. In addition, the European central and virtual biobank of BIOMARKAPD we established is a valuable resource for researchers to validate emerging biomarkers for neurodegenerative disorders.

Furthermore, the rapidly increasing prevalence of dementia with little progress in treatment development and high costs for testing treatments emphasizes the need to prescreen individuals suitable for treatment intervention studies. Studies in this thesis may be useful for pharmaceutical companies to design future treatment trials and to help identify individuals suitable for treatment.

Products

The main products of this thesis are the results that may guide future studies and clinical practice. Almost all manuscripts have been published in scientific journals and presented at international conferences. Furthermore, for future biomarker development a biobank has been set-up of CSF and blood samples for the European study BIOMARKAPD funded by JPND. This biobank was set up to support the validation of emerging biomarkers for diagnosis of neurodegenerative diseases and promotes data sharing. The stimulate use of the biobank a website has been made available for BIOMARKAPD sample requests (http://jpnd.arone.com/) and we described the biobank in a publication.

Innovation and implementation

In this thesis, we investigated established but also innovative measures with computerized tests, emerging CSF biomarkers, and emerging risk factors. This may aid in our understanding of the pathophysiological mechanism of AD and predictors of disease expression in order to facilitate treatment development. In addition, it aids in our understanding of clinical disease progression, which may benefit patient care. The knowledge obtained by our studies can be used for planning for future studies by researchers and drug developers.