Neuropsychiatric symptoms in Alzheimer's disease

KNOWLEDGE VALORIZATION

In this chapter, the possibilities of valorization of the results presented in this thesis will be described. Valorization of research is the process of creating value from knowledge[1]. In other words, how can the obtained knowledge from this research be of relevance for the society in general, and how it can be (clinically) implemented?

Societal and/or economic relevance

The prevalence of age-related diseases, such as dementia, increases as a function of the growing aging population and an increased recognition and attention of its signs and symptoms from the public, sciences, practitioners and care providers[2]. An estimated 254.000 individuals in the Netherlands met diagnostic criteria for dementia in 2015, and this number is expected to triple by 2050[3]. This makes dementia for many high-income countries, among which the Netherlands, a health- and social-care priority[3].

In addition to the well-known cognitive impairments part of Alzheimer's disease (AD), it is now acknowledged that nearly all patients with AD develop one or more neuropsychiatric symptoms (NPS) over the course of the disease[4, 5]. The implications of AD, and NPS in particular, are multifold. For one, there are direct consequences for the person with AD and his or her caregiver(s), in terms of high distress, increased burden, and lower quality of life (QoL)[6, 7]. An indication of the impact of NPS can be drawn from the finding that presence of NPS are a major determinant of (earlier) nursing home placement, leading to high long term institutionalization costs[8]. In fact, the societal costs of NPS in dementia are staggering: a third of dementia care costs has been attributed to the direct management of NPS, because of the greater use of health services, acute and respite hospitalization, and medication costs[8-10]. Additional costs are for example due to time spend by caregivers supervising the patient, which is time spent away from work or leisure activities[11]. These increased costs of dementia care are even significant in mild cognitive impaired community dwelling people[11]. Thus, NPS have a significant impact on patient and society, in terms of burden and costs.

As there is no cure or disease-modifying treatment available for AD, one major goal is to increase and maintain QoL, for example by prevention and management of NPS. However, the multifactorial and heterogeneous nature of NPS makes this challenging. It is therefore necessary to increase our understanding of the underlying mechanisms of the development of NPS. More knowledge on the ideopathogenesis of NPS has implications for treatment development, as different patients with different NPS might benefit from different treatment strategies. Indeed, it was shown that AD pathology was cross-sectionally associated with anxiety and apathy (albeit indirectly, via disease severity) and with the development of depression and apathy over time, but not with symptoms such as agitation

and irritability. Although the research designs do not allow for differentiation between cause-and-effect, all studies showed that NPS are very common across the disease spectrum. Knowledge and acknowledgement of the high prevalence of NPS may result in better recognition, distinction and earlier detection of NPS. It also further underlines the importance of NPS, next to cognitive decline, as hallmarks of AD, even in prodromal phases of the disease.

Target groups

Mrs. J. is a 76-year old woman with mild AD dementia. A year after her first visit to the memory clinic, she is brought again by her daughter, because of concerns about behavioral changes. Her daughter mentions her decline in interest and sad mood: "Whereas she used to enjoy helping my father with household chores, she now sits in the living room and watches tv. She doesn't even seem to enjoy visits from the grandchildren." Mrs. J. smiles appropriately in social situations but does not further engage in conversations or other activities. Although the daughter is worried about her mother and demands further medical assessment, her father feels that as long Mrs. J. seems content, he should respect her decisions to no longer participate in daily activities.

Various hypotheses have been posed to explain NPS in AD. It has been suggested that NPS are risk factors for AD or that NPS non-cognitive symptoms of the disease, which implies that NPS should be associated with underlying AD pathology[2]. The results of this thesis suggest that Mrs. J's. development of symptoms of apathy experienced by Mrs. J. are (partly) explained by AD pathology.

Knowledge on the relationship between AD pathology and NPS is in the first place of relevance for patients, caregivers, and clinicians. Even when not (yet) apparent, it would be beneficial to educate patient and caregivers that NPS are also considered symptoms of the disease. Oftentimes, NPS are not mentioned spontaneously by patient and caregiver, such that raising awareness of such symptoms will lead to earlier detection and recognition, in turn leading to earlier possibilities of interventions. One can think of modifiable factors other than neurobiology such as unmet needs (where a patient has lack of meaningful activities), factors related to caregiver (negative communication styles), or the environment (lowered stress threshold, difficulties with processing and responding to environmental stimuli). In the case study, the family of Mrs. J. might benefit from professional help to discuss strategies to encourage increased activity. Further, the frustration of Mrs. J.s daughter might be lessened if she is educated about the nature of apathy as part of the disease.

The findings of this thesis are of relevance to health-care professionals as the burden of interpreting clinical and biomarker data rests with them. Perhaps it is not only the patient

and caregiver that should be educated about NPS, but also clinicians. In the presence of AD pathology, increased attention must be given to individualized care options as these patients are at risk for developing NPS. Prior studies showed that the presence of NPS is related to faster progression of the disease, which raises the interesting hypothesis that treatment or management of these symptoms can act as a protective factor for disease progression. The studies in this thesis further showed that the trajectories which individual NPS take are heterogeneous, underlining that cross-sectional assessment of affective symptoms is insufficient. In a like manner, it was shown that QoL does not follow a monotonic trajectory over time. That is, QoL increased after first visit to the memory clinic, after which it showed a decline. It is thus important that clinicians give continuous attention to QoL, even in light of first improvements.

The findings are also of relevance for policy makers and care managers. In the Netherlands, the majority of people with dementia live at home, i.e. are "community-dwelling"[3, 12], which is also promoted by the government via the "Long-term Care Act" (Wet Langdurige Zorg, 2015). This has resulted in various legal frameworks involved with the organization and financing of dementia care, and thus many health care professionals are involved. Although the Dutch Elderly Care Physician guidelines for NPS in dementia[13] recommend the multidisciplinary analysis of NPS, the fragmentation of primary dementia care (and thus involving many health care professionals) does not facilitate coordinated care planning. Thus, it must be emphasized that once NPS have been identified, health care professionals must act together and communicate in order to manage them.

The findings of this thesis provide a framework for researchers in the AD-NPS field. The large heterogeneity observed in prior studies with regard to measurement instruments and definitions suggests that AD-NPS research would likely benefit from uniform definitions. One such framework is the recently proposed AT(N) classification system, where patients are scored according to three biomarker categories[14]. It is not meant as a (clinical) diagnostic system but as a descriptive and standardized system, agnostic to temporal ordering of underlying mechanisms[14]. However, in the current phase of exploring NPS as an expression or cause of the disease, it is crucial to understand how individual biomarkers evolve over time and interact with each other or NPS. One must be aware of the consequences of utilizing arbitrary cut-offs in such research phase. Another implication of this thesis is the identification of the heterogeneity of study designs, instruments and definitions used. More effort must be made to reach consensus on definitions of the concepts under examination.

For pharmaceutical companies who aim to find treatment strategies, this research is of relevance as it suggests that patients with more AD pathology are most likely to develop NPS over time. This means that inclusion criteria can be employed for such clinical trials, selecting those with lower amyloid and higher tau levels. However, this thesis also shows

that, in order to answer any question on causality, we need to extend the amount of measurements on NPS and biomarkers. That is, more frequent follow-up measurements on both parameters would allow modeling of the two in a parallel manner. We also need better characterizations of the psychiatry history of patients, such that in parallel to retrospective self-reports, we use data that is stored with the general practitioner.

Innovation and products

Throughout this thesis, we tried to step away from the thought that estimating one population-average approximates the truth. In the first part of this thesis a comprehensive state-of-the-art view on the association between AD biomarkers and NPS was offered. By combining information from all relevant studies, the systematic review and meta-analysis can provide more precise estimates of the effects than those derived from individual studies[15]. This also allowed the generation of hypotheses that were tested in following chapters, for example, regarding differential effects along the AD disease spectrum. In addition, the nature and relative strength of the associations between AD biomarkers and NPS were explored more in-depth by including cross-sectional mediation analyses. Further, we utilized an innovative statistical technique by which subjects could be grouped into latent classes on the basis of similarities in their trajectories over time. Following the line of reasoning from personalized medicine - where diagnosis and treatment is based on individual characteristics - , we should aim to conduct research in such way that we are able to incorporate multiple indicators and zoom in on an individual level. The main product of this thesis is the implication of the results for clinical practice and future research, as described above. Finally, the collection, cleaning and harmonization of multi-center data done for this thesis (and documentation thereof) will allow future researchers to utilize these beautiful datasets.

Schedule and implementation

A large part of the results of this research has been disseminated via publications in international, peer-reviewed, scientific journals and presentations at international conferences. The results have implications for our ongoing research, where we continue the examination of the association of AD pathology with behavioral changes, for example in the concept of mild behavioral impairment (MBI[16]), in collaboration with the Johns Hopkins University School of Medicine research group at the department of Psychiatry and Behavioral Sciences, Division of Geriatric Psychiatry and Neuropsychiatry. Further, we aim to expand the examination of trajectories of individual NPS, for example by including interactions with other NPS.

REFERENCES

1. Campus BMH. Valorisation guidelinefor UM/MUMC+ researchers Version: 22/12/2017 [Available from: https://www.brightlands.com/application/files/8215/2578/3490/BL_MHC_Valorisation_guideline.pdf.

2. Peters ME, Lyketsos CG. Beyond memory: a focus on the other neuropsychiatric symptoms of dementia. The American Journal of Geriatric Psychiatry. 2015;23(2):115-118. 10.1016/j.jagp.2014.11.002

3. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimer's & Dementia. 2013;9(1):63-75. e62.10.1016/j.jalz.2012.11.007

4. Aalten P, de Vugt ME, Jaspers N, Jolles J, Verhey FR. The course of neuropsychiatric symptoms in dementia. Part I: findings from the two-year longitudinal Maasbed study. International Journal of Geriatric Psychiatry. 2005;20(6):523-530. 10.1002/gps.1316

5. Monastero R, Mangialasche F, Camarda C, Ercolani S, Camarda R. A systematic review of neuropsychiatric symptoms in mild cognitive impairment. Journal of Alzheimer's Disease. 2009;18(1):11-30. 10.3233/JAD-2009-1120

6. Black BS, Johnston D, Morrison A, Rabins PV, Lyketsos CG, Samus QM. Quality of life of community-residing persons with dementia based on self-rated and caregiver-rated measures. Quality of Life Research. 2012;21(8):1379-1389. 10.1007/s11136-011-0044-z

7. Cheng S-T. Dementia caregiver burden: A research update and critical analysis. Current Psychiatry Reports. 2017;19(9):64. 10.1007/s11920-017-0818-2

8. Schnaider Beeri M, Werner P, Davidson M, Noy S. The cost of behavioral and psychological symptoms of dementia (BPSD) in community dwelling Alzheimer's disease patients. International Journal of Geriatric Psychiatry. 2002;17(5):403-408. 10.1002/gps.490

9. Balestreri L, Grossberg A, Grossberg GT. Behavioral and psychological symptoms of dementia as a risk factor for nursing home placement. International Psychogeriatrics. 2000;12(S1):59-62. 10.1017/S1041610200006773

10. Lyketsos CG, Carrillo MC, Ryan JM, Khachaturian AS, Trzepacz P, Amatniek J, et al. Neuropsychiatric symptoms in Alzheimer's disease. Alzheimers & Dementia. 2011;7(5):532-539. 10.1016/j.jalz.2011.05.2410

11. Herrmann N, Lanctôt KL, Sambrook R, Lesnikova N, Hébert R, McCracken P, et al. The contribution of neuropsychiatric symptoms to the cost of dementia care. International Journal of Geriatric Psychiatry. 2006;21(10):972-976. 10.1002/gps.1594

12. Volksgezondheidenzorg.info. https://www.volksgezondheidenzorg.info/onderwerp/dementie/cijfers-context/huidige-situatie: RIVM: Bilthoven; 2019

13. (verenso) Vvso. 2018 [Available from: https://www.verenso.nl/richtlijnen-en-praktijkvoering/richtlijnendatabase/probleemgedrag-bij-mensen-met-dementie.]

14. Jack C, Bennett D, Blennow K, Carrillo M, Dunn B, Elliott C. NIA-AA research framework: towards a biological definition of Alzheimer's disease. Alzheimers & Dementia. 2018;14(4):535-562. 10.1016/j.jalz.2018.02.018

15. Antman EM, Lau J, Kupelnick B, Mosteller F, Chalmers TC. A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts: treatments for myocardial infarction. JAMA. 1992;268(2):240-248. 10.1001/jama.1992.03490020088036

16. Ismail Z, Agüera-Ortiz L, Brodaty H, Cieslak A, Cummings J, Fischer CE, et al. The Mild Behavioral Impairment Checklist (MBI-C): a rating scale for neuropsychiatric symptoms in pre-dementia populations. Journal of Alzheimer's disease. 2017;56(3):929-938