Alzheimer's disease: a report from the 7th Kuopio Alzheimer symposium

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The 7th Kuopio Alzheimer symposium was held on 11–13 June, 2015, in Kuopio, Finland and attracted ~250 attendees from 14 different countries around the world. The theme for the symposium in its seventh year was 'From mechanisms to prevention and intervention of Alzheimer's disease'. The 3-day international scientific symposium composed of seven oral sessions and a poster session. The program, spanning from molecular mechanisms to prevention, prediction, diagnosis and treatment of Alzheimer's disease, provided a forum for the attendees to share their research, network and to obtain a comprehensive overview of the current status and future directions of research into Alzheimer's disease.

The intensive program of the 7th Kuopio Alzheimer symposium consisted of a broad range of oral and poster presentations presented over the 3 days that covered a wide variety of topics related to molecular mechanisms, prevention, prediction, diagnosis, intervention and care within Alzheimer's disease (AD). The latest findings in these timely topics were presented in seven oral sessions entitled 'New insights into neurodegeneration', 'Diagnosis and prediction of Alzheimer's disease: update on biomarker studies', 'New advances in imaging', 'Technology-supported diagnosis and care', 'Novel approaches towards prevention', 'Population-based prevention studies' and 'Novel approaches in clinical treatment studies'. In addition, 38 posters were presented in the poster session. The extensive program cannot be fully covered here, but we aim to report some symposium highlights describing the latest trends and findings in the field.

AD has been identified as a global health priority as the growing burden of the disease will challenge the current healthcare systems and national economies [1,2]. AD is the most common cause of dementia in the elderly but, together with other memory diseases, it may also affect individuals who still actively participate in working life [2]. AD is a progressive disease with a long duration. The pathological changes in the brain start up to 20 years before the occurrence of any clinical symptoms. The current medications used to treat Alzheimer's patients can alleviate the symptoms, but at present there are no treatments able to stop or slow AD progression [3]. Moreover, AD patients often concomitantly have other diseases, such as Type 2 diabetes or cardiovascular diseases, which may influence the pathogenic processes at the molecular level and aggravate AD progression and symptoms [4–6]. Disease mechanisms in AD, its prevention, early diagnosis and treatment have been under intense research over the last few decades [7]. Today the focus of research has shifted toward early and accurate prediction of developing AD in individual patients. Identifying people at risk for developing dementia and prioritizing them for treatment or enrollment into interventions and clinical trials may help us identify ways to prevent or even cure this complex disease [8].

KEYWORDS

- Alzheimer's disease
- biomarkers • brain imaging
- diagnosis • prediction
- prevention • randomized controlled trial

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These important and challenging issues were also discussed during the 7th Kuopio Alzheimer symposium.

Executive Director J Georges from Alzheimer Europe (Luxembourg) opened the symposium with an address entitled 'Making dementia a European Priority'. To date, 36 associations in 31 countries are part of Alzheimer Europe, a nonprofit organization aimed at improving the care and treatment of Alzheimer patients. In June 2006, Alzheimer Europe and its member organizations adopted the Paris Declaration of the Political Priorities of the European Alzheimer movement. Here, the associations called on European institutions and national governments to make dementia a public health priority, to develop national action plans on dementia and to promote funding for AD research. Georges presented some of the achievements of Alzheimer Europe's campaign at both EU and national level, including European Commission Alzheimer's Initiative in 2009. These initiatives have led to European research collaboration through several EU-funded programmes. For example, the FP7 programme (2007–2013) provided funding for EUR 555 million on dementia and EUR 327 million on AD. These topics remain continued priority also for the ongoing Horizon 2020, the EU Framework Programme for Research and Innovation, which was launched in 2014. Georges also discussed the continued development of national and EU level Alzheimer plans and dementia strategies. These aim, for example, at better coordination of European research initiatives and programs in the field of dementia, appointing an EU dementia coordinator, global actions on dementia, active involvement of people with dementia, caregivers and Alzheimer associations and exchanging good practices to provide good care and eventually cure for AD. Alzheimer Europe's latest campaign, launched in October 2014 in its Glasgow Declaration, calls for the development of a European dementia strategy and for greater coordination with global initiatives at G7, WHO and OECD level.

The keynote speaker Dr J Streffer from Janssen Pharmaceutica NV, Beerse (Belgium) discussed the need for large databases to provide answers to understanding the pathogenesis and treatment of AD and other memory diseases. The development of new therapeutic approaches for the management of memory diseases and dementia has been hampered by a lack of detailed understanding of the complex and multifactorial

pathophysiology of these diseases. The molecular composition of the neuropathological hallmark lesions of AD, composed of β -amyloid and tau, are already well known. However, other proteins and different metabolic, vascular and genetic factors are likely to be involved in AD pathogenesis and may function as risk factors or as triggers or drivers of its pathology. These have been previously investigated in small study cohorts in individual centers, but in these studies the composition of risk profiles and shared pathology varies significantly. Currently, the field is moving toward the use of biomarker-targeted multicenter cohorts (e.g., Alzheimer's Disease Neuroimaging Initiative and AddNeuroMed), targeted data sharing (e.g., for large genome-wide association studies or selected biomarkers) as well as growing consortia (e.g., European Medical Information Framework-AD [EMIF-AD]). The power of these large datasets for providing detailed information on disease pathogenesis and potential new therapeutic targets needs multidisciplinary collaborations including basic science, epidemiology, clinical specialties, statistics and information technology. Multidisciplinary approaches are needed to ensure the selection of the suitable cohorts and datasets, analysis methods and data interpretation. Dr Streffer is a leader at the EMIF-AD platform, where the approach is to provide an integrated, efficient framework for consistent reuse and exploitation of currently available patient-level data in a variety of formats to support novel research. This facilitates access to more than 50,000 participants in AD research studies and more than 50,000,000 Europeans through electronic medical records. Biomarker studies are presently underway with this approach in EMIF-AD at a scale and depth of data, which has not been previously possible. Additionally, there is great potential for real-world data analysis, postmarketing effectiveness studies and examining repurposing therapeutic approaches (as an example). In the European Prevention of Alzheimer's dementia Initiative, which is part of the Innovative Medicines Initiative Joint Undertaking and includes about 35 partners from private and academic sectors within six country/regional areas, the use of large databases has been taken to the next step with a collaborative approach toward drug development. In European Prevention of Alzheimer's dementia, different drug trials will have a shared control group, against which the efficacy of each drug will be compared. This allows quick

identification of promising drugs, which may then be targeted to detailed scrutiny.

The second keynote speaker, Professor M Kivipelto from Karolinska Institute, Stockholm (Sweden) emphasized the importance of lifestyle factors in the management of dementia. The author presented data from the first large, long-term randomized controlled trial, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER). FINGER study revealed that a multidomain intervention may indeed improve or maintain cognitive function in elderly, who are at risk of developing dementia. The study involved 1260 participants of 60–77 years of age who had a slightly elevated risk for memory disorders. One group of participants was given conventional lifestyle advice, while the other group received personalized counseling related to nutrition, exercise and cognitive training and support for the management of cardiovascular disease risk factors. After 2 years' follow-up, the risk of decline in cognitive performance was 31% higher in the control group than in the intervention group receiving enhanced counseling. In addition, significant improvements in body mass index, dietary habits, physical activity and quality of life were observed in the intervention group. The participants in the FINGER study are followed further for the next 5 years to achieve long-term follow-up data from the effects of lifestyle intervention. Kivipelto also coordinates the European MIND-AD (Multimodal preventive trials for AD: toward multinational strategies) project, in which a similar intervention will be conducted among persons already suffering from mild cognitive impairment (MCI). Together with enhanced lifestyle counseling, a nutrition supplement designed for the needs of the aging brain will be tested.

The development of novel predictive AD biomarkers by employing proteomic approaches to the analysis of plasma and cerebrospinal fluid samples was described by Dr I Pike, the Operative Manager from Proteome Sciences plc (Cobham, UK). Dr Pike and his team have identified over 40 candidate biomarkers for early diagnosis and as surrogates of cognitive decline and hippocampal atrophy. Recently, they have reported that AD severity and progression could be classified based on changes in plasma concentration of 16 proteins in a large cohort of over 1100 individuals, including patients with AD or MCI and controls. Furthermore, they

have developed a new blood-based test using proteomics approach to assay a panel of 10 proteins, which can at 87% accuracy identify memory patients likely to develop AD within 1 year. Changes in the concentrations of these proteins are indicators of a fast progression of the disease. The test has not yet been evaluated for early diagnosis in the general population, but it could be utilized in clinical trials for example for selecting patients with the greatest risk of developing AD to the trial. Currently, Dr Pike uses novel proteomic workflows to find the earliest tissue-derived biomarkers in cerebrospinal fluid. With this enhanced mass spectrometry workflow, they have been able to identify multiple candidate biomarkers of neuroinflammation, synaptic dysfunction, altered metabolism and other pathways reported to be affected in AD. These biomarkers have the potential to serve as very early diagnostic tests but require further validation in large cohorts, clarified Dr Pike.

Molecular brain imaging helps both in the diagnostics and differential diagnostics of memory diseases as well as in the monitoring of treatment response. In the future, brain imaging may also play a role in the selection of a personalized treatment for patients, said Professor J Rinne from Turku PET Centre, Turku (Finland). PET is a functional imaging technique, which allows versatile investigation of various brain functions, such as blood flow, glucose metabolism, neurotransmitter function, neuroinflammation and allows visualization of AD-related protein aggregates, such as β -amyloid and tau. Studies with several β -amyloid imaging ligands have shown that patients with AD show a clear increase in tracer uptake in frontal, parietal, temporal cortices and in the posterior cingulate gyrus. In patients with MCI, positive β -amyloid imaging predicts conversion to AD. On the other hand, PET imaging has indicated that a surprisingly large share of patients do not show evidence for β -amyloid aggregation, suggesting that these patients may not benefit from β -amyloid-targeting therapies. Imaging tau aggregation in AD and various tauopathies might help in their diagnosis and differential diagnosis. Fluorodeoxyglucose-PET can be utilized in studies of neuronal and synaptic function. Patients with AD typically show symmetrical temporoparietal hypometabolism in fluorodeoxyglucose-PET. Similar changes have been detected also in patients with MCI, in healthy individuals carrying apolipoprotein E

4 allele and in healthy elderly individuals with a familial history for AD. Similar hypometabolism in healthy elderly has been shown to predict future global cognitive decline. Frontotemporal degeneration, another group of neurodegenerative syndromes, predominantly shows frontal and anterior temporal hypometabolism, which aids in differential diagnosis from AD. Imaging studies regarding neuroinflammation have so far produced controversial results. Increased astrogliosis has been found at MCI stage but not in AD, suggesting that astrogliosis is an early event in the pathophysiology of AD. The current developments in the brain imaging ligands and techniques suggest that longitudinal multitracers imaging could reveal the temporal relationship between the various pathological processes in AD in the future.

In addition to the issues described above, many other timely topics were discussed during the symposium, including results from other ongoing joint EU-funded projects. One of these was the LipiDiDiet study that addresses the impact of nutritional lipids on neuronal and cognitive performance in aging, AD and vascular dementia. The Healthy Ageing Through Internet Counseling in the Elderly project, in turn, aims to develop an interactive internet-based intervention to improve cardiovascular risk management to prevent incident cardiovascular disease, cognitive decline and dementia. Virtual Physiological Human: Dementia Research Enabled by IT and PredictND (aiming at developing tools and means for earlier,

evidence-based diagnosis of a range of neurodegenerative diseases) are examples of projects that develop novel tools to aid clinicians both in differential diagnostics of memory diseases and in predicting progression to dementia. These projects also accelerate the reuse and future implementation of previous trial results.

In conclusion, the 7th Kuopio Alzheimer symposium served as a platform for obtaining a comprehensive overview of the current status and future directions of AD research from molecular and cellular disease mechanisms to prediction, prevention, diagnosis and treatment and care of the patients. Active discussion of these important topics will pave the way for maintaining AD and other dementias as a global healthcare priority and enable collaborative efforts for developing accurate predictive biomarkers and identifying novel targets for intervention and management of these devastating diseases.

The program and abstracts of the 7th Kuopio Alzheimer symposium can be found at the symposium website [9].

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