2018

A report from the 8th Kuopio Alzheimer Symposium

Haapasalo, Annakaisa

Future Medicine Ltd

Tieteelliset aikakauslehtiartikkelit
© Future Medicine Ltd
All rights reserved
http://dx.doi.org/10.2217/nmt-2018-0029

https://erepo.uef.fi/handle/123456789/7921

Downloaded from University of Eastern Finland's eRepository
A report from the 8th Kuopio Alzheimer Symposium

Annakaisa Haapasalo* and Mikko Hiltunen

1 A.I. Virtanen Institute for Molecular Sciences and 2 Institute of Biomedicine, University of Eastern Finland, Kuopio, Finland.

*Corresponding author:

Annakaisa Haapasalo, PhD
Associate Professor in Molecular Neurodegeneration
A.I. Virtanen Institute for Molecular Sciences
University of Eastern Finland
Neulaniementie 2
70211 Kuopio, Finland
Tel: +358 40 355 2768
E-mail: annakaisa.haapasalo@uef.fi

Running title: Report from 8th Kuopio AD symposium
Abstract

The international Kuopio Alzheimer Symposium was organized by the University of Eastern Finland in Kuopio, Finland on June 6-8, 2018 for the 8th time. Approximately 300 researchers in the fields of neuroscience and neurology from 12 different countries around the world gathered to Kuopio to hear and discuss about the latest insights into the mechanisms and comorbidities and novel approaches for diagnosis, prediction, prevention and therapies of Alzheimer’s disease (AD) and other neurodegenerative diseases. The two-day international program on June 7-8 included a keynote session, five oral scientific sessions, and a poster session. The international symposium was preceded by a “Memory Day” on June 6, held in Finnish and targeted to Finnish health care professionals, including doctors, psychologists, and nurses, who work daily with patients suffering from neurodegenerative diseases.
The 8th Kuopio Alzheimer Symposium hosted 25 talks by international leading scientists and 49 poster presentations given by PhD students, postdocs and other researchers. The themes in the symposium covered novel advances related to disease mechanisms, model systems and translational medicine applications, biomarker studies, brain imaging, technology-supported diagnosis and care, population-based prevention studies, co-morbidities, and clinical treatment studies.

Alzheimer’s disease (AD), the most common cause of dementia in the elderly, and other neurodegenerative diseases generate a growing global health challenge as the portion of the aging population in the societies continuously increases worldwide [1]. Aging is the most important risk factor for dementing brain diseases. On the other hand, some neurodegenerative disorders, such as frontotemporal lobar degeneration (FTLD), whose main clinical subtype is frontotemporal dementia (FTD), typically have an earlier onset age than AD. Therefore, they may affect people already at working-age [2]. Management of neurodegenerative diseases and their comorbidities, such as cardiovascular diseases, high blood pressure, type 2 diabetes (T2D), or brain traumas, which are other major risk factors for neurodegenerative diseases, becomes increasingly important and has been recognized as a health care priority internationally and nationally in different countries [1,3]. A general consensus is that identification of the patients or even individuals with an increased risk of having a neurodegenerative disease as early as possible is key to successful treatment and prevention of AD and other neurodegenerative disorders. Combining data from biomarker and brain imaging studies with information of the individual’s genetic background will likely be applied in the risk assessment, early diagnosis, prevention, and choosing appropriate treatment options for neurodegenerative diseases at personalized level in the future. However, early identification and intervention are complicated by the current lack of suitable specific and sensitive biomarkers, which could be used in the diagnosis or prediction of the diverse neurodegenerative diseases. The currently available treatments offer only relief to the symptoms (e.g. behavioral or psychiatric symptoms) and support for the neuronal function, but so far, no disease-modifying therapies that would be able to decelerate or halt the disease progression exist for treating the patients suffering from
neurodegenerative diseases. One likely reason for this is that the molecular disease mechanisms underpinning neurodegeneration are highly complex and not yet well understood. Thus, novel model systems, including those directly derived from the patients themselves, are needed to decipher disease mechanisms and aid the discovery of novel biomarker candidates and therapeutic targets. Also, preventive measures that could be applied globally are essential in the management of neurodegenerative diseases in the future. These complex and challenging topics were covered in the presentations of the 8th Kuopio Alzheimer Symposium. Here, we provide a summary of the oral presentations of the symposium.

**Keynote lectures**

In 2018, 112 drugs are in the development pipeline for AD. Of these, 23 agents (in 25 trials) are in phase I, 63 agents (in 75 clinical trials) in phase II, and 26 agents (in 35 trials) in phase III [4]. Sixty three percent are disease-modifying drugs, 22 % are symptomatic cognitive enhancers and 12 % address neuropsychiatric or behavioral symptoms [4]. Despite the large number of trials, many initially promising clinical trials have been discontinued because of the lack of efficacy or adverse side effects over the last decades. Prof. Hilkka Soininen from the University of Eastern Finland, Kuopio, Finland, underlined in her keynote lecture on “*Highlights of clinical Alzheimer research*” that development of treatments and prevention are major challenges in AD research. Therefore, it is essential to focus on earlier start of the treatment of the patients so that a patient with the right diagnosis gets the right drug at the right time. By using biomarker data, AD can be diagnosed earlier. Furthermore, participants could be recruited into drug trials in an earlier phase of the disease, which is important when investigating effects of disease-modifying treatments. Large international consortium studies related to brain imaging, biomarker and genetics have produced an ample amount data. The temporal sequence of disease progression in AD, suggested also by previous brain imaging and biomarker studies, was recently confirmed by *Dominantly Inherited Alzheimer Network* (DIAN), reporting that in AD familial mutation carriers, β-amyloid (Aβ) starts accumulating over two decades before the symptoms, followed by brain metabolism decline six years later, and
brain atrophy about five years before symptoms [5]. Therefore, international consortia aiming at better understanding of the early stages of AD and testing interventions that are targeted to AD prevention before the clinical symptoms occur are extremely important. Prof. Soininen summarized that key issues in the successful drug development and treatment of AD patients in the future are the need for disease-modifying drugs, new drug targets and proper target validation, targets suggested by epidemiological studies that have been confirmed in randomized control trials (RCTs) and use of combination therapies.

The other keynote lecture was given by Prof. Daniel M. Michaelson from Rabin Institute of Neurobiology, Tel Aviv University, Israel, on “Converging approaches to the development of anti-APOE4 therapy”. Apolipoprotein E4 (APOE ε4) is the strongest genetic risk factor for AD, increasing the risk of AD by approximately four-fold [6]. Prof. Michaelson suggested that APOE ε4, if combined with a “second hit”, such as aging, head injury, Aβ, tau, or synaptic stress, is harmful to the neurons and causes synaptotoxic effects. Using the CRISPR-Cas9 gene editing technology to specifically target APOE ε4 in mice and crossing these targeted replacement (TR) mice with α-synuclein-deficient mice, Prof. Michaelson and colleagues found that the mice displayed decreased levels of specific synaptic markers and increased levels of Aβ42, hyperphosphorylated tau and the astrocyte marker glial fibrillary acidic protein (GFAP), corroborating their “second hit” hypothesis. The mice also showed cognitive deficits in behavioral tests. Prof. Michaelson’s team has also used the APOE ε4 TR mice to investigate the effects of immunization therapy using specific anti-ApoE4 monoclonal antibodies and treatments targeting lipidation, as they had earlier found that ApoE4 protein is hypolipidated. Repetitive immunization of young ApoE4 TR mice resulted in the accumulation of ApoE-antibody complexes in the brain and the reversal of the Aβ42, tau, and synaptic pathological alterations and cognitive deficits. Moreover, treatment of young APOE4-TR mice with CS-6253, a brain-penetrant agonist of the lipidation protein ATP-binding cassette transporter (ABCA1), reversed the hypolipidation of ApoE4 and counteracted the APOE4-driven brain and cognitive impairments. Altogether, Prof. Michaelson’s team has identified potential new APOE4-related therapeutic approaches, which might show translational potential also in AD patients.
Patients with different neurodegenerative diseases are neuropathologically characterized by accumulation of protein aggregates in the affected brain areas [7]. Dr. Vesa Kiviniemi from University of Oulu, Finland, presented insights into enhancing brain clearance of aggregated proteins through the recently discovered glymphatic system [8]. Recent findings suggest that dysfunction of the glymphatic system leads to a slow accumulation of proteins and neurodegeneration. While the glymphatic system and factors affecting clearance in brain are under intensive debate, research elucidating these factors may hold great potential for identification of novel therapeutic approaches.

Normally, glymphatic system pulsation is at least partially driven by the heart to clear up the brain, but in AD brain, the glymphatic system pulsation shows an impairment. This finding is supported by e.g. novel brain magnetic resonance imaging (MRI) signal analyses and advances in optoelectronic imaging enabling the monitoring of dynamic free water changes in the human brain. Studies in AD mouse models indicate that increasing of blood-brain barrier (BBB) permeability with focused ultrasound (FUS) can facilitate the removal of the accumulated proteins from the brain and reverse memory loss. The research team of Dr. Kiviniemi now uses advanced optoelectronic brain monitoring to measure the status of glymphatic brain system at various manipulations of BBB. They aim at investigating tailored techniques for BBB opening to reveal the role of BBB permeability in brain clearance and allow optimization of therapies targeted to brain areas with insufficient clearance.

Technological advances allowing the use of skin fibroblasts or blood cells to generate induced pluripotent stem cells (iPSC) and further neurons or other brain cells, such as astrocytes or microglia, from the patients have revolutionized the field of modeling different neurological diseases and offer excellent options to screen new biomarker and drug candidates [9-12]. Prof. Jari Koistinaho from the University of Eastern Finland, Kuopio, and University of Helsinki, Finland, described utilization of the iPSC technology to generate astrocytes from AD patients harboring the exon 9 deletion in the \textit{PSEN1} gene (\textit{PSEN1}\textsubscript{E9}). He showed that the \textit{PSEN1}\textsubscript{E9} mutant astrocytes, which manifest key hallmarks of AD pathology including increased A\textsubscript{\textbeta} production, altered cytokine release and
dysregulated calcium homeostasis, also show impaired mitochondrial metabolism and glutathione
and lactate secretion concomitantly with increased reactive oxygen species production after
neuroinflammatory stimulation. When co-cultured in 3D cultures together with neurons from a healthy
donor, these mutant astrocytes, but not the gene-corrected isogenic control astrocytes generated
using CRISPR/Cas9 technology from the same PSEN1ΔE9 mutation-carrying patients, led to
impairments of synaptic responses in the neurons. These data provide novel insights into the
important and previously poorly known contribution of astrocytes to AD pathology in humans.

Drug development against AD has faced many drawbacks as many drug trials have been
stopped because of the lack of efficacy or adverse side effects, such as liver toxicity. Although
treatment of patients with already established dementia has been unsuccessful, stopping Aβ
deposition by β-secretase (β-site amyloid precursor protein cleaving enzyme, BACE1) inhibition
appears a promising treatment strategy for AD. Dr. Ulf Neumann from Novartis Institute for
Biomedical Research, Basel, Switzerland, said that the current hypothesis is that BACE1 inhibition
treatment (or other Aβ-targeting therapies) needs to be started at the early phases of Aβ deposition,
before the onset of significant neurodegeneration. He introduced the BACE1 inhibitor CNP520,
which had undergone previous careful pharmacokinetic, metabolism, and long-term toxicological
profiling. Clinical phase I and phase IIa studies in healthy elderly volunteers established its safety,
tolerability, and active dose range. The phase I studies showed a dose- and time-dependent
reduction of cerebrospinal fluid (CSF) Aβ42 by CNP520 and its activity was unchanged by the APOE
genotype. Therefore, the profile of CNP520 supports its use in prevention studies of AD. Currently,
clinical phase II/III studies are ongoing, which test CNP520 effects in a cognitively healthy population
with enhanced risk to develop AD. Participants were included based on their age, APOE ε4
genotype, and for those carrying a single APOE ε4 allele, elevated brain amyloid. The dose selection
for CNP520 in long-term clinical trials aims at avoiding full enzyme inhibition, good safety margins,
and good separation of exposure and effect.

Prof. Dieter Edbauer from German Center for Neurodegenerative Diseases (DZNE), Munich,
Germany, discussed the early role of dipeptide repeat (DPR) proteins in C9orf72 hexanucleotide
repeat expansion-associated amyotrophic lateral sclerosis (ALS)/FTD. This repeat expansion is the most common genetic cause of ALS and FTD [13,14]. His team has previously shown that the expanded repeat RNA is translated in all reading frames into five DPR proteins by an unconventional mechanism, but it is still unclear how toxicity of the repeat RNA and the DPR proteins are driving neurodegeneration in patients. The $C9orf72$ repeat expansion carriers show brain atrophy and deficits in neuropsychological tests already 20 years before disease onset [15] and the DPR proteins can be detected in the CSF of presymptomatic $C9orf72$ expansion carriers many years prior to disease onset [16]. To elucidate the potential early role of DPR proteins in ALS/FTD, Prof. Edbauer’s group has generated cellular and animal models expressing the DPR proteins individually. They showed that mice overexpressing the neurotoxic poly-glycine-alanine (poly-GA), the most abundant DPR species in patient brains, display progressive brain poly-GA protein and phosphorylated TDP-43 pathology and progressive motor deficits and gait abnormalities. Mice expressing poly-GA at high levels showed regional neurodegeneration that was preceded by microglial activation. Using cryoelectron tomography, the Edbauer team found that poly-GA protein aggregates sequestered large amounts of proteasomes, which are essential components of the protein degradation machinery in cells, and inhibit their function, leading to stalled protein degradation. All in all, the data indicate that early DPR expression contributes to the prodromal symptoms and disease progression of $C9orf72$ hexanucleotide repeat expansion-carrying patients and one potential underlying mechanism driving neurodegeneration could be compromised proteasomal protein degradation, leading to toxic protein accumulation in the brain.

II Scientific session - New developments in diagnostic and predictive biomarkers in Alzheimer’s disease and other neurodegenerative diseases

Dr. Marylene Simon from Roche Diagnostics GmbH, Penzberg, Germany and Roche Diagnostics International, Rotkreuz, Switzerland opened the session by discussing automated CSF biomarker assays in AD management. She described a study where CSF samples collected from patients with mild cognitive impairment (MCI), subjective cognitive decline, and AD from the Swedish
BioFINDER and the Alzheimer’s Disease Neuroimaging Initiative (ADNI) cohort were analyzed using the Roche Elecsys® Aβ42 immunoassay. The results were compared to positron emission tomography (PET) brain Aβ imaging data to test the potential of the CSF biomarker status to predict clinical progression, measured by the change in the Clinical Dementia Rating Sum of Boxes (CDR-SB) score from baseline to 24 months. They found that CSF biomarker data from the Elecsys® immunoassay analyses and Aβ PET imaging showed high concordance. Moreover, biomarker positive and negative groups showed significantly different progression rates over the 24-month follow-up. These findings suggest that the Elecsys® CSF biomarker assays show potential in the diagnosis and prediction of patients with suspected AD or MCI.

Tau pathology is a hallmark of several neurodegenerative diseases and CSF tau and phosphorylated tau levels, in addition to those of total tau and Aβ42, are used as clinical biomarkers for AD and other neurodegenerative diseases [17]. Assoc. Prof. Kina Höglund from University of Gothenburg, Sweden, presented novel CSF tau fragments as potential candidate biomarkers for tauopathies, including AD. Her team hypothesizes that secreted tau fragments may reflect disease-specific proteolytic cleavages of tau. They have developed a technique where CSF samples are immunoprecipitated using specific antibodies against tau followed by mass spectrometry (MS) analysis. They also have generated end-specific tau antibodies and developed enzyme-linked immunosorbent assay (ELISA) or single molecule array (Simoa) assays using these antibodies. For each tau fragment, the clinical relevance in CSF studies was evaluated by comparing the levels between AD and other tauopathies to healthy controls and correlating the data to tau PET brain imaging. The research team found that amino-terminal tau fragments of 20-25 kDa in size provided the best separation between AD patients and controls. Specific fragments were found increased in the CSF of AD patients as compared to the controls and these fragments were enriched in the tau neurofibrillary tangles (NFTs) in the brain. Interestingly, patients with progressive supranuclear palsy (PSP), another tauopathy and a rare form of FTLD, showed decreased levels of these fragments. Future studies will reveal whether these fragments prove to be useful biomarkers in the clinics.

Prof. Martin Ingelsson from Uppsala University, Sweden, discussed improved discrimination between healthy control subjects and patients with cognitive decline. His group applied ELISA and
MS-based shotgun proteomics to investigate the classical biomarkers and the CSF proteome in patients with AD, FTD, or mild cognitive impairment (MCI; some of which converted to AD during follow-up) and in non-demented control subjects. They observed that 12 MS-based biomarkers can slightly improve identification of AD patients. Furthermore, combination of ELISA and MS-based assays allowed a good identification of FTD patients. Prof. Ingelsson concluded that their findings suggest that the addition of new biomarkers in a model-based approach can improve the value of analyzing CSF to distinguish control subjects from patients with cognitive decline.

Prof. Pieter Jelle Visser from Maastricht University, The Netherlands, introduced the EMIF-AD Multimodal Biomarker Discovery Study for identifying diagnostic and predictive markers for AD in the predementia stage. In this study, the diagnostic and prognostic value of proteins in CSF and plasma, brain atrophy patterns on MRI and genetic markers are tested. Existing samples and brain scans from altogether 1200 Aβ-positive and negative individuals with normal cognition, mild cognitive impairment (MCI) or mild dementia from 11 existing European cohort studies central proteomic, metabolomic, genomic, epigenomic and imaging analyses. The average follow-up was 2.3 years. Prof. Visser concluded that by combining already existing data and samples, it is feasible to perform large-scale multimodal biomarker discovery analyses. Also, including CSF and possibly plasma analyses of recently introduced new biomarkers, whose levels are altered in AD patients including neurofilament light chain (NFL), neurogranin, and YKL40, a chitinase-like glycoprotein associated with inflammation and tissue remodeling, might show potential diagnostic value in the future.

III Scientific session - New technologies in neurodegenerative diseases, including imaging, disease models and neuroinformatics

Insulin resistance (IR) is suggested to be a risk factor for AD and cognitive decline [18]. Previous studies have also shown that cardiovascular risk factors, such as increased cholesterol or blood pressure, are associated with AD and cognitive decline later in life [19]. However, association among midlife IR and late-life cognitive performance, cerebrovascular lesions, and brain Aβ accumulation is unclear. Dr. Laura Ekblad from Turku PET Center, Finland, discussed about PET imaging of individuals who did not have dementia but had an increased homeostatic model
assessment of IR (HOMA-IR) score at midlife. Sixty individuals, of whom half had elevated HOMA-IR score (HOMA-IR+) at midlife and the other half normal HOMA-IR score (HOMA-IR-), underwent neuropsychological testing, MRI, and PET imaging using the Aβ-binding Pittsburgh compound B (PiB). In both groups, 50% of the individuals carried the APOE ε4 allele. In the HOMA-IR+ group, 60% of the individuals and in the HOMA-IR- group, 33% of the individuals showed positive PiB-PET imaging results. Concomitantly, the HOMA-IR+ group displayed lower executive function and processing speed in the neuropsychological tests. Moreover, in the HOMA-IR+ group, the APOE ε4 carriers showed enhanced PiB binding in the PET imaging. Dr. Ekblad summarized that their findings now show that midlife IR is an independent risk factor for brain Aβ accumulation and decreased cognitive function in elderly individuals, who do not have dementia. An unexpected observation was that individuals with IR did not have more cerebrovascular lesions than those without IR.

Dr. Jyrki Lötjönen from Combinostics Ltd, Tampere, Finland, described the PredictND project developing tools for helping the clinical diagnosis of patients with neurodegenerative diseases. These tools aid clinicians in interpreting different types of data coming from multiple sources (biomarkers, brain imaging etc.) in a systematic and objective manner to support disease diagnosis and prediction. The PredictND project developed a clinical decision support tool including two main components. The image quantification module provides a set of imaging biomarkers from MRI images. The decision support module compares all the patient’s data to data originating from a large number of previously diagnosed patients and evaluates their similarity to those of the different etiologies (AD, FTD, dementia with Lewy bodies, vascular dementia, or cognitively normal individuals) or to patients known to progress to dementia. Approximately 800 patients from four memory clinics (Amsterdam, Copenhagen, Kuopio and Perugia) and from different studies with retrospective data underwent a prospective study using PredictND. Although statistically significant difference was not observed in diagnostic accuracy, the tool improved the confidence of clinicians in decision making. Multiple studies using PredictND showed that automatically computed imaging biomarkers combined with other data provide valuable information both for differential diagnostics and prediction of disease progression. The project has demonstrated that clinical decision support
systems based on modern machine learning techniques can be useful in helping to interpret patient data in clinical practice.

Examples of low-cost tests for decision support in neurodegenerative disease were given by Dr. Mark van Gils from VTT Technical Research Center of Finland. His team has compared the relationship of Muistikko web-based cognitive test battery, computer games, and gait analysis with standard neuropsychological assessments used in clinical practice. Dr van Gil’s team developed a global cognitive score (GCS) based on age, sex, Mini Mental State Examination (MMSE) test, and different other cognitive tests. Then, they developed regression models to estimate GCS from Muistikko and computer game features. For the gait analysis, time and frequency features from 3D-accelerometry were studied and correspondence analysis with established cognitive measures was performed. The results of the study including over 300 patients from memory clinics in Amsterdam, Copenhagen, Kuopio and Perugia indicated that both Muistikko test and game-based features showed a good correspondence with the GCS, and gait-related features, such as speed, variance and regularity, correlated with different levels of cognitive impairment. The study by Dr. van Gils and colleagues indicated that low-cost measurements, which can be easily done during everyday living, are able to provide valuable information related to cognitive impairment. These kinds of measurements that can be done in informal settings may offer a valuable, low-cost addition to the existing set of tools to support decision making and evaluation of risk of cognitive decline in the management of dementing diseases.

The last two talks of the session moved from diagnostic tools to new developments in disease modeling systems. Assist. Prof. Doo Yeon Kim from Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, USA, described novel biological model systems to help in the dissection of molecular disease mechanisms and drug development in AD. His team has recently developed a 3D “Alzheimer’s on a dish” human neural culture model that recapitulates robust AD-like Aβ aggregation and hyperphosphorylated tau NFT accumulation [20]. From the original set up, they have now developed the model further by creating a sophisticated 3D culture model based on the co-culture of human neuronal precursor cells, astrocytes, and microglia in microfluidic devices, allowing them to include the previously missing AD-related neuroinflammatory elements into the
model. This new model system has now been utilized in the dissection pathogenic mechanistic
cascades that mediate Aβ-induced tau phosphorylation. Assist. Prof. Kim also described an
exploratory high-throughput AD drug screening project using the 3D model. Here, primary screening
of a drug library of almost 2500 compounds containing all the US Food and Drug Administration
(FDA)-approved drugs was performed. The screening yielded 39 hits that strongly decreased
accumulation of insoluble hyperphosphorylated tau with or without affecting Aβ accumulation. The
Kim research group has now shown that the 3D human model system recapitulating the key
pathological features of AD, Aβ accumulation an NFT formation, can be utilized to screen e.g. γ-
secretase modulators (GSMs), FDA-approved drugs for their repurposing, or testing the potency of
hit molecules from in silico drug screenings in alleviating these pathologies.

Prof. Tiago Outeiro from University Medical Center Goettingen, Germany, described cell-
based systems to model Parkinson’s disease (PD, [21]) -related α-synuclein pathologies. α-synuclein
is a synaptic protein, which is misfolded and undergoes aggregation in PD brains. Prof. Outeiro’s
group uses novel imaging approaches and has developed tissue-clearing and expansion microscopy
(ExM) techniques to overcome the detection limit of normal light microscopy. Using these novel
imaging approaches, it is possible to achieve 10-12 times better resolution and nanoscale precision
of the target cells or tissues. By using these techniques, they have revealed novel interactions of α-
synuclein. These techniques will be useful in understanding the underlying mechanisms and protein
features and interactions that result in protein misfolding and subsequent aggregation in different
neurodegenerative diseases characterized by protein aggregation, including PD.

IV Scientific session - Co-morbidities of neurodegenerative diseases

The fourth session was opened by Prof. Wiesje van der Flier, from VU University Medical
Center, The Netherlands, who said that the advances in diagnosis of AD using MRI, CSF biomarkers,
and PET Aβ-imaging are among the biggest successes in AD research, but often the diagnosis is
made only in the late stages of the disease. She underlined that a better and earlier diagnosis would
be very beneficial so that the patients could receive help quicker and more effectively. Alzheimer’s
biomarkers in daily practice (ABIDE) is a Dutch project, which aims to improve AD diagnosis in
memory clinics by promoting effective application of MRI, CSF biomarker, and PET data for
diagnosis of MCI and AD, e.g. by using the \textit{PredictND} clinical decision support system, and taking
into account patients' perspective and wishes on their use. Focus groups comprising patients,
caregivers and professionals provide support for the notion that decisions on diagnostic testing
should be made in a setting of shared decision making. Patients and caregivers also stress that they
would value more specific information on what the results of the diagnostic tests mean for them. In
the ABIDE project, individualized risk models that allow estimation of probabilities of progression
from MCI to dementia, taking patients' characteristics into account, have been developed. The risk
models will be integrated in an easy-to-use app, called the ADappt, which aims to improve doctor-
patient communication and provide support for the diagnostic conversation. Prof. van der Flier
concluded that with the development of new diagnostic tests, we enter an era allowing translation of
the scientific findings to daily clinical practice. Thus, tools supporting the diagnostic process may
catalyze quicker and more effective diagnosis.

Dr. Alina Solomon from the University of Eastern Finland, Kuopio, Finland, talked about the
urgent need for developing tools to help to quantify dementia risk and prevention potential in clinical
trials. The currently available dementia risk scores can be based on only non-modifiable risk factors,
such as age or genetic background, only modifiable risk factors, such as lifestyle-related factors or
vascular, metabolic or other manageable comorbidities, or combinations of these. All these different
types of risk scores have been previously used in dementia prevention trials testing pharmacological
or non-pharmacological interventions with varying results. Thus far, the most successful intervention
model has been based on modifiable lifestyle factors. In this model, multidomain interventions
targeting real-life multifactorial risk profiles instead of a single risk factor have been carried out. So
far, only a few studies have attempted to bridge the gap between prediction and prevention of
dementia. Validated prediction tools are essential in both clinical trials and everyday clinical practice
to aid identification individuals, who are at risk of developing dementia, and to direct them to the
interventions that will be the most beneficial for them. Dr. Solomon concluded that development of
prediction tools that can estimate the individual’s dementia risk, but also his or her prevention
potential is important.
Different comorbidities of neurodegenerative diseases were also discussed in the session. Profs. Ville Leinonen from Kuopio University Hospital and Oulu University Hospital, Finland, and Etsuro Mori from Osaka University, Japan, described in their presentations the normal pressure hydrocephalus (NPH), a disease which is characterized by enlarged ventricles, gait difficulty and urinary incontinence [22]. A subset of the patients respond well to shunt treatment and their clinical symptoms are relieved. NPH often co-occurs with AD and some NPH patients show molecular comorbid features to AD, such as Aβ pathology in brain. Patients with enlarged ventricles often show cognitive deterioration, but the final specific diagnosis may vary. Some NPH patients may develop other co-occurring neurodegenerative diseases later in life. Prof. Leinonen described that the Kuopio NPH registry contains of more than 900 patients with enlarged ventricles and a diagnosis of possible idiopathic NPH (iNPH). Long-term follow-up indicated that 73% of non-shunted patients with enlarged ventricles, 63% shunted iNPH patients who did not respond to treatment, and 46% iNPH patients who were initially responsive to shunting developed dementia. Based on the registry data, Prof. Leinonen’s team was able to make an estimation of the long-term cognitive outcome of shunted iNPH patients. Approximately 25% of the patients is estimated to remain cognitively intact, 25% to suffer mild cognitive impairment, 20% to have AD dementia, 20% vascular dementia, 10% NPH-related dementia, and occasional cases to have some other neurodegenerative disease. Prof. Leinonen concluded that the fact that dementia, caused by various neurodegenerative diseases, occurred frequently in patients with ventricular enlargement emphasizes the need for a careful and collaborative diagnostic evaluation by neurologists and neurosurgeons. Moreover, the shunted iNPH patients should undergo clinical follow-up to test for shunt patency in the case of cognitive deterioration.

Prof. Etsuro Mori corroborated in his talk that the only effective treatment for iNPH is CSF diversion with ventriculo-peritoneal (VP) or lumbar subarachnoid space-peritoneal (LP) shunt. He introduced the SINPHONI-2 study, carried out in Japan, which is an RCT comparing shunt and conservative therapy. The SINPHONI-2 study has clearly demonstrated the benefits of LP shunt. However, iNPH patients are often misdiagnosed and inadequately treated. It has been recognized that a characteristic deformity termed disproportionately enlarged subarachnoid space...
hydrocephalus (DESH), which is apparent on MRI or computer tomography (CT) scans, is a valuable biomarker for differential diagnosis of iNPH and AD and for predicting the efficacy of shunting. Then again, iNPH and AD often co-occur, and the co-occurring AD may diminish the effect of shunting. Thus, it needs to be evaluated if shunting is beneficial for patients with comorbid AD and iNPH. On the other hand, the efficacy of the shunt therapy may be larger than that of any currently available drugs for treating AD in these patients. Prof. Mori also mentioned that iNPH therapy that may alleviate dementia might give useful cues for developing treatments for AD.

One of the important risk factors for AD and dementia, as shown by many epidemiological studies, is T2D [18]. Several studies have provided evidence for insulin resistance in the brains of AD patients, but the common molecular mechanisms linking AD and T2D are still largely unknown. Prof. Mikko Hiltunen from the University of Eastern Finland, Kuopio, Finland, and his team have utilized large population-based cohorts to identify such links. They have used the METabolic Syndrome In Men (METSIM) and the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) cohorts to correlate AD-associated genetic factors to parameters related to cardiovascular health and metabolism. It has previously been shown that carriers of the A673T variant of amyloid precursor protein gene APP scored better in cognitive tests and displayed less age-related cognitive decline over time, suggesting that this genetic variation is protective against AD [23]. Prof. Hiltunen and his team identified carriers of the APP-A673T variant from the METSIM cohort and showed that they had 30% lower levels of Aβ40 and Aβ42 in the plasma as compared to the controls. The mechanism explaining the decreased levels of Aβ in the A673T variant carriers is that it makes APP a less favorable substrate for BACE1, leading to reduced BACE1 cleavage of APP and subsequently decreased Aβ production. The APP-A673T variant carriers did not show any adverse changes in the metabolic or cardiovascular parameters, which is encouraging from the point of view of designing Aβ-reducing therapies, such as BACE1 inhibition, against AD. Using the METSIM and FINGER cohorts, the Hiltunen team moved on to assess peripheral effects of APOE ε4 and found a strong association with decreased levels of plasma high-sensitivity C-reactive protein (hs-CRP). Also, reduced hs-CRP and plasma Aβ42 levels showed an association independently of the APOE status, suggesting that Aβ might possess anti-inflammatory effects as
suggested by some previous studies. Finally, to interrogate the mechanistic link between AD and insulin signaling, Prof. Hiltunen and his group used transgenic APP/PS1 AD model mice and their wild-type littersmates that underwent intranasal insulin treatment. The intranasal insulin administration was found to specifically activate signaling of Akt2, a protein kinase, which belongs to the PI3K/Akt pathway downstream of the insulin receptor, in the hippocampus of wild-type mice, but not in APP/PS1 mice, suggesting that brain insulin signaling may be compromised in AD. Altogether, the data from Prof. Hiltunen and colleagues suggest that large population-based cohorts are suitable for assessing the cardiovascular and metabolic effects of AD-associated genetic variants and emphasize the disadvantageous link between AD-associated genetic components and insulin signaling in the brain.

V Scientific session - Prevention and therapies of neurodegenerative diseases

The topic of the last session of the symposium dealt with the latest advances in prevention studies and therapies of neurodegenerative diseases and dementia. Prof. Miia Kivipelto from Karolinska Institute, Stockholm, Sweden and University of Eastern Finland, Kuopio, Finland, discussed about multidomain interventions to prevent dementia. Mounting evidence indicates that multidomain lifestyle interventions, which simultaneously target several risk factors and mechanisms, possess large potential to prevent or postpone late-life cognitive impairment and dementia. The FINGER study is the first large trial indicating that a multidomain lifestyle intervention can prevent cognitive impairment in the elderly [24] and it represents a pragmatic model for dementia prevention. In another ongoing project, Multimodal preventive trials for Alzheimer Disease: towards multinational strategies (MIND-AD), the FINGER intervention model is tested in patients who have prodromal AD and lifestyle or vascular risk factors. Furthermore, prompted by the positive results of the FINGER study, similar studies have been started in different populations and settings in Europe, USA, China, Singapore, and Australia. To promote synergy across these trials and optimize the efforts towards dementia prevention, the World-Wide FINGERS Initiative (WW-FINGERS) was recently launched. WW-FINGERS is an interdisciplinary network aiming at sharing experiences and data and planning joint initiatives focusing on dementia prevention. It is expected that WW-FINGERS
will facilitate synergistic use of data from different countries and enable rapid implementation of knowledge and definition of effective and feasible prevention programs for diverse populations globally.

Prof. Ingmar Skoog from the University of Gothenburg, Sweden, discussed the implications of prevention and treatment related to preclinical AD. Previous studies suggest that midlife vascular risk factors, such as high blood pressure and/or cholesterol, T2D, atrial fibrillation and myocardial infarction, and lifestyle-related factors, including leisure intellectual and physical activities, cardiovascular fitness, and dietary habits, influence the risk of late-life AD. Also, proneness to stress, number of adverse life events, neurotic personality, and lower education at midlife increase the risk of AD later in life. Although several longitudinal population-based studies have reported that midlife high blood pressure and body mass index (BMI) are linked to AD, these start to decline 5-10 years before disease onset, possibly because of AD-related brain changes that may influence the regulation of blood pressure. These changes in the brain are present more than two decades before the clinical onset of the disease as shown by brain imaging and neurochemical studies. This idea is supported by the findings that 23% of cognitively normal 70-year-olds showed pathological Aβ42 levels, 33% pathological tau and 10% pathological phospho-tau levels in the CSF. In total, 46% these cognitively normal individuals displayed at least one pathological CSF AD marker. Prof. Skoog emphasized that, based on these findings, the association between AD biomarkers and risk factors needs to be clarified. This information can then be used to evaluate when the suitable prevention measures and treatment need to be initiated.

Prof. Christopher Chen from the National University of Singapore presented Asian perspectives for the prevention and therapy of neurodegenerative diseases. He referred to a recent report from the Lancet Commission on Dementia Prevention, Intervention and Care [25], which listed nine potentially modifiable risk factors for dementia and calculated for them a weighted population attributable fraction (PAF), an estimate of the proportion of cases of dementia that could be avoided if exposure to individual risk factors were eliminated, supporting the idea of launching multidomain lifestyle interventions globally. Prof. Chen introduced a pilot SINgapore GERiatric intervention study.
to reduce physical frailty and cognitive decline (SINGER) as part of the WW-FINGERS initiative. The SINGER study was designed to establish the most appropriate multidomain lifestyle interventions for Singaporean seniors, optimize recruitment procedures, and provide a strong basis for a proposed two-year RCT. He also introduced novel Asian therapeutic approaches to AD, including traditional Chinese medicines. For example, the ongoing Alzheimer’s disease THerapy with NEuroaid (ATHENE) study, which is a randomized, double-blind and placebo-controlled trial, assesses the safety and efficacy of Neuroaid II, a natural product combining several active ingredients including herbal extracts, in patients with mild to moderate AD stable on acetylcholinesterase inhibitors (AChEI) or memantine. Studies in cellular and animal models of brain injury have indicated that Neuroaid II has neuroprotective and neuroproliferative properties and may modulate APP processing and tau hyperphosphorylation. Moreover, it has shown beneficial effects on cognitive function in AD patients with better tolerability and safety profile than standard AChEIs.

Dr. Tiia Ngandu from National Institute for Health and Welfare (THL), Finland, talked about adherence to multidomain preventive interventions and shared experiences from real-life implementation of these interventions. She said that multimodal lifestyle interventions can be demanding for the participants. However, the participants must adequately adhere to the trial protocol in order to achieve lifestyle changes that will provide cognitive benefit. Currently, there is no golden standard for defining good or poor adherence to the intervention and not much is known about the adherence to non-pharmacological interventions. In practice, adherence and intervention outcome likely show a dose-response relation. Recent results from European lifestyle trials have identified potential determinants of adherence to the interventions and characteristics of the intervention and the participant may influence adherence. The positive results of the lifestyle intervention trials in dementia prevention now call for actions to implement the prevention activities into real-life settings. Dr. Ngandu mentioned that here, identification of target groups for the interventions, identification of the facilitators and obstacles for achieving and maintaining healthy lifestyle changes, and close collaboration with the key stakeholders responsible for the implementation activities are essential.
Prof. Nenad Bogdanovic from Karolinska University Hospital, Stockholm, Sweden, discussed about therapeutic strategies against AD, which would be much needed for the treatment of patients with AD and other neurodegenerative diseases. The currently approved drugs in the clinical use for mild-to-severe AD or moderately severe-to-severe AD are the AChEIs donepezil, galantamine, and rivastigmine, and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine. Prof. Bogdanovic summarized that the current drug studies have largely depended on the amyloid cascade hypothesis targeting Aβ, but also tau and small molecules are being investigated. The diagnostic groups in the drug trials comprise patients at different phases of the disease, including at-risk populations (in prevention studies) and preclinical or pre-symptomatic AD, prodromal AD, or mild-to-moderate AD. In these studies, the amyloid pathway is targeted using vaccination and antibodies against Aβ or and inhibitors or modulators of γ-secretase and β-secretase. Prof. Bogdanovic mentioned that even though the link between Aβ deposition and tau pathology remains elusive, the downregulation of tau-related toxicity might provide clinical benefit. It is widely acknowledged that a large problem in developing drugs against AD is the multifactorial nature of dementia and the fact that the elderly individuals often have other comorbidities, including concurrent vascular dementia and different types of neurodegenerative lesions. As the successful treatment against AD is still waiting to be discovered, Prof. Bogdanovic said that meanwhile the current treatment options could be improved by e.g. individualization and adjustment of current AChEI-related therapy to age, gender and APOE genotype.

Prof. Anders Wimo from Karolinska Institute, Stockholm, Sweden, concluded the symposium by discussing health economic aspects of dementia prevention. The significantly positive results of the FINGER multidomain lifestyle intervention study related to cognition and function in the elderly have generated hope that such prevention programs would be able to impact the future numbers of people with dementia. However, the long-term effects or long-term cost effectiveness of these studies are still unknown. Prof. Wimo’s team has used the FINGER study to perform health economic simulation with a comprehensive sensitivity analysis. They also compared prevention simulations and the simulations for potential cost effectiveness of hypothetical disease-modifying treatments for
AD. In these studies, they have identified the number needed to treat (NNT) in a prevention program like FINGER and its related costs to avoid one case of dementia, as well as the incremental cost-effectiveness ratio with QALYs (quality adjusted life years) as the outcome. In all the simulations, the prevention was proven cost-effective, implicating that primary dementia prevention is potentially cost-saving or cost-effective. These results suggest that dementia prevention programs may be able to affect the number of people suffering from dementia and be economically beneficial in the future.

In summary, the 8th Kuopio Alzheimer symposium provided a comprehensive overview of the latest advances and future directions of the research into AD and other neurodegenerative diseases. The program comprised oral and poster presentations related to the molecular and cellular mechanisms of neurodegeneration, novel, sophisticated model systems and their translational potential, identification of new predictive and diagnostic biomarker candidates, new technologies and tools for decision support, insights into comorbidities with other diseases, and global efforts in the prevention and treatment of AD and other neurodegenerative diseases. This research altogether aims at better understanding of the mechanisms of neurodegeneration and at developing efficacious methods for early identification, diagnosis, and treatment of patients with neurodegenerative diseases or even identification of individuals at increased risk of dementia for prevention and therapeutic studies. Ultimately, the knowledge gained from these studies is expected to lead to the discovery of optimal, timely, and individualized prevention and treatment options to help management of neurodegenerative diseases worldwide.

The program and abstracts of the 8th Kuopio Alzheimer symposium can be found at the symposium website [26].
References


