DND Dementia and Neurocognitive Disorder

Review Article

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Executive Summary of the 2021 International Conference of Korean Dementia Association: A Report From the Academic Committee of the Korean Dementia Association

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ABSTRACT

Recently, aducanumab, a beta amyloid targeted immunotherapy, has been approved by the US Food and Drug Administration for the treatment of Alzheimer's dementia (AD). Although many questions need to be answered, this approval provides a promising hope for the development of AD drugs that could be supported by new biomarkers such as blood-based ones and composite neuropsychological tests that can confirm pathologic changes in early stages of AD. It is important to elucidate the complexity of AD which is known to be associated with other factors such as vascular etiologies and neuro-inflammation. Through the second international conference of the Korean Dementia Association (KDA), researchers from all over the world have participated in the exchange of opinions with KDA members on the most up-to-date topics. The Academic Committee of the KDA summarizes lectures to provide the depth of the conference as well as discussions. This will be an important milestone to widen the latest knowledge in the research of AD's diagnosis, therapeutics, pathogenesis that can lead to the establishment of future directions.

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Conflict of Interest

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INTRODUCTION

The Korean Dementia Association (KDA) has been holding an international academic conference every two years since 2019. This international conference of KDA 2021 (IC-KDA2021) was held as an on-line and off-line hybrid symposium due to coronavirus disease 2019 (COVID-19). IC-KDA2021 was held for 2 days on October 1 and 2, 2021. It was attended by 508 people from 23 countries. A total of 144 posters were exhibited, despite the unfortunate situation of COVID-19. It has established itself as an international academic conference representing the field of dementia in Korea.

IC-KDA2021 drew attention in that it was held during the height of controversy over the first FDA-approved treatment for Alzheimer's disease (AD) in 18 years. It is well known that the FDA has granted accelerated approval for aducanumab. It gives us a number of challenges to be solved. At the same time, it gives us a new hope that AD may be controllable. From the meaning of 'accelerated approval', this disease modifying drug has not yet demonstrated its clinical effects. However, this decision is worthwhile from the perspective that it suggests the role of surrogate end points as a primary outcome measure tool for drug development. In other words, it means that biomarkers are no longer confined to diagnostic markers, but are expanding their scopes to evaluate prognosis of disease and measure drug effects.

With this background, IC-KDA2021 drew attention from many researchers and scholars because it dealt with the current status and future research direction of biomarkers and drug development related to AD under the theme of 'Current and Future Directions of Dementia Research'. IC-KDA2021 was composed of 6 scientific sessions, 4 plenary lectures, and 2 luncheon symposiums and poster session for both days. For the first time, AD International (ADI) session for discussion of 'dementia care and global action in the COVID-19 situation' was held on the second day.

Based on the theme of "'Current and Future Directions of Dementia Research", scientific sessions were divided into the following 6 topics: neuroimaging with imaging genetics, neuro-inflammation, vascular contribution to dementia, public health and epidemiology, blood-based biomarkers, and neuropsychology. Each session had three sub-topics. Four plenary lectures were presented by invited leading scholars in those fields. It was a good opportunity to look at major research achievements from various angles. At the ADI parallel symposium, two scientific sessions were held under the title of 'Beyond COVID: New thinking on the future of dementia care' and 'Global Progress on addressing Dementia'.

The purpose of this article is to provide a comprehensive understanding of the most advanced knowledge in the field of AD by summarizing key events presented in IC-KDA 2021.

SESSION 1. NEUROIMAGING WITH IMAGING GENETICS

In this session, imaging genetics was introduced as an emerging data science field. Interactive analysis of brain imaging and genetic data provided new insights into phenotypic characteristics and genetic mechanisms of normal or diseased brain structure and function. Additionally, imaging genetics provided the development strategy of new diagnostic therapeutic and preventative approach. Building an open science research ecosystem to accelerate AD therapy development was also introduced.

From imaging genetics to precision medicine for AD (Andrew J. Saykin, Bloomington, IN, USA)

Dr. Saykin provided an overview of imaging genetics with respect to precision medicine of AD. Brain imaging was started from a region of interest. It was then expanded to the circuit and whole brain. Genetics was initially focused on candidate genes. Its spectrum was also widened to biological pathways and genome-wide analysis. As AD is a complex disease with more than 20 implicated biological pathways, it is necessary to find out each pathway and potential targets.[1] Multi-omics data enable a system biology focusing on complex interactions within biological systems of AD using a holistic approach. To combined multi-omics with imaging, large scale new collaborative studies such as ENIGMA Consortium, AI4AD, and ADNI4 based on open science, data sharing, and new analysis are to be started.

Genetic variants beyond amyloid and tau in AD (Yong Jeong, Daejeon, Korea)

In his presentation, Dr. Jeong showed single nucleotide polymorphisms (SNPs) associated with cognitive decline independent of Aβ and tau pathology in AD. Using ADNI dataset (http://adni.loni.usc.edu/), genome-wide association study (GWAS) was conducted to identify SNPs associated with individual cognitive function while controlling for the level of Aβ and tau followed by gene ontology analysis of SNP-associated genes. As a result, identified SNPs negatively affected cognitive function partially through cortical thinning on the brain. Furthermore, a bioinformatics analysis showed that the identified SNPs are related to glutathione metabolism. This finding provides insight into the complexity of AD pathogenesis and supports the growing literature on the role of glutathione in AD.[2]

Genome-wide association study of cerebral β-amyloid deposition and cerebral atrophy in Gwangju Alzheimer's and related dementias (GARD) cohort (Kunho Lee, Gwangju, Korea)

Dr. Lee performed a GWAS on brain cerebral Aβ levels measured using amyloid positron emission tomography (PET) from GARD cohort to identify novel genetic loci associated with cerebral Aβ deposition. As a result, CPAMD8 (rs12975891, p=4.42×10−9) was newly identified. According to homology modelling and molecular dynamic simulations, it might inactivate some proteins and result in the prevention of amyloid oligomerization. These findings and follow-up studies will likely improve our understanding of genetic pathways related to cerebral Aβ deposition that leads to AD.

PLENARY SESSION 1: AD DRUG DEVELOPMENT: CURRENT AND FUTURE (JEFFREY CUMMINGS, UNIVERSITY OF NEVADA LAS VEGAS, Las Vegas, NV, USA)

There are six approved drugs for AD treatment, including four cholinesterase inhibitors, one N-methyl-D-aspartate (NMDA) receptor antagonist (Memantine), and one anti-amyloid antibody (Aducanumab). A total of 126 agents are currently in clinical trials according to the 2021 Alzheimer's drug development pipeline.[3] Of these drugs, 104 agents (83% of all agents) are disease-modifying therapies.

Dr. Cummings introduced the current and future drugs for AD by classifying them into three major classes. The first class is cognitive enhancing agents, including cholinesterase inhibitors (Donepezil, Rivastigmine, and Galantamine), NMDA receptor antagonist

(Memantine), and the mixed form of Donepezil and Memantine (Namzaric). In addition to these approved drugs, there are several experimental agents. The second class is agents used for treating neuropsychiatric syndromes in AD. Various agents for treating agitation are in clinical trials. Orexin antagonists such as Suvorexant are in clinical trials for sleep problems. Recently, the Harmony trial[4] showed successful results of Pimavanserin for treating psychosis in dementia with its results under review by the FDA. The third class is disease-modifying agents focusing on amyloid processing in AD. This class includes gamma secretase inhibitors/modulators (e.g., Tarenflurbil and Semagacestat) and β-site amyloid precursor protein cleaving Enzyme (BACE) inhibitors (e.g., Verubecestat, Atabecestat, and Lanabecestat). It has been shown that some BACE inhibitors can worsen the cognition in trials with adverse events such as hepatotoxicity. Monoclonal antibodies can target monomers, oligomers, or plaque amyloid. Several anti-amyloid monoclonal antibodies are in clinical trials currently. Aducanumab[5] attacks oligomer and plaque amyloid. It is the first approved disease-modifying therapy for AD. Although phase 3 EMEGRE and ENGAGE trials were halted after efficacy and futility analyses suggested no benefit, additional data showed that the EMERGE trial had met the primary outcome on the Clinical Dementia Rating—sum of box score with marked plaque lowering.[6,7] The FDA allowed its accelerated approval based on preliminary evidence that the plaque lowering is likely to predict clinical benefit. The FDA required a phase 4 confirmatory trial to produce additional evidence on the clinical benefit of aducanumab. The accelerated approval of monoclonal antibody has a profound effect on AD drug development. It is based on a biomarker which predicts clinical benefit. Aducanumab was approved based on its ability to lower of plaque amyloid on amyloid PET. Other monoclonal antibodies such as Donanemab, Lacanemab, and Gantenerumab are currently in clinical trials for AD.

There are also monoclonal antibodies and small molecules that target tau biology. Monoclonal antibodies that target cell-to-cell transmission and small molecules that target tau biology include aggregation inhibitors, autophagy inducers, microtubule stabilizers, and epichaperone inhibitors.[8]

In the current drug pipeline, there are many drugs with novel mechanisms of action, including drugs involving genetics and epigenetics, microbiome-based therapeutics, antioxidants, anti-inflammatory or anti-infective agents, drugs targeting neuronal hyperactivity, metabolic agents, and vascular-directed agents. The pace of AD drug development will increase. Some monoclonal antibodies are candidates for obtaining accelerated approval for AD treatment.

PLENARY SESSION 2. NEUROVASCULAR DYSFUNCTION IN COGNITIVE IMPAIRMENT: FROM BENCH TO BEDSIDE (COSTANTINO IADECOLA, WEILL UNIVERSITY, NEW YORK, NY, USA)

Dementia is growing at an alarming rate worldwide. Although AD is the leading cause, over 50% of individuals diagnosed with AD have vascular lesions at autopsy. There has been an increasing appreciation of the pathogenic role of vascular risk factors in cognitive impairment caused by neurodegeneration.

Midlife hypertension is a leading risk factor for late-life dementia.[9] Hypertension alters cerebrovascular structure, impairs major factors regulating the cerebral microcirculation, and promotes Alzheimer pathology. Experimental studies have identified brain perivascular macrophages (PVMs) as the major free radical source mediating neurovascular dysfunction of hypertension. PVMs represent a distinct population of resident brain macrophages that play key homeostatic roles. They also have the potential to generate large amounts of reactive oxygen species (ROS). This effect was mediated by an increase in blood-brain barrier permeability that allowed angiotensin II to enter the perivascular space and activate angiotensin type 1 receptors in PVMs, leading to the production of ROS through the superoxide-producing enzyme NOX2.

Recent evidence has indicated that high dietary salt may also induce cognitive impairment. Dietary habits and vascular risk factors can promote both AD and cognitive impairment caused by vascular factors. Furthermore, accumulation of hyperphosphorylated tau, a microtubule-associated protein and a hallmark of Alzheimer's pathology, is also linked to vascular cognitive impairment (VCI). In mice, a salt-rich diet can lead to cognitive dysfunction associated with a nitric oxide deficit in cerebral endothelial cells and cerebral hypoperfusion. Here, Iadecola and Gottesman[9] report that dietary salt can induce hyperphosphorylation of tau followed by cognitive dysfunction in mice. These effects can be prevented by restoring endothelial nitric oxide production. Nitric oxide deficiency can reduce neuronal calpain nitrosylation and result in enzyme activation, which in turn can lead to tau phosphorylation by activating cyclin-dependent kinase. Salt-induced cognitive impairment was not observed in tau-null mice or in mice treated with anti-tau antibodies, despite persistent cerebral hypoperfusion and neurovascular dysfunction. These findings demonstrate a causal link between dietary salt, endothelial dysfunction, and tau pathology, independent of hemodynamic insufficiency. Avoidance of excessive salt intake and maintenance of vascular health may help stave off vascular and neurodegenerative pathologies that underlie dementia in the elderly.

SESSION 2. NEUROINFLAMMATION, TO BE OR NOT TO BE?

AD is a multi-faceted neurodegenerative disease with underlying pathologies that extend well beyond the widely recognized accumulation of amyloid beta (Aβ) and neurofibrillary tangles. Together with abnormal protein deposits, it is now established that neuroinflammation represents the third hallmark found in AD patients' brains. Based on this concept, this session was focused on roles of neuroinflammation in the aging brain both in healthy and pathological conditions, including AD and amyotrophic lateral sclerosis (ALS). We had presentations and discussion together with three speakers.

Neuroinflammation and pathological sequelae in AD (Thor Stein, Boston University, Boston, MA, USA)

The presentation by Dr. Thor Stein was focused on apolipoprotein E (APOE) ε4-mediated inflammatory responses. To test the hypothesis that microglia and AD-implicated cytokines might be differentially associated with AD pathology based on the presence of APOE ε4, his lab examined the dorsolateral frontal cortex from deceased participants within a community-based aging cohort. He found that cellular density of Iba1 was positively associated with tau pathology only in APOE ε4 positive participants. This result suggested that APOE ε4 mediated an altered inflammatory response and increased tau pathology. He also showed that APOE ε2 AD cases revealed a novel mechanism involving complement 4

in AD development and that repetitive head impacts could lead to vascular injury, microglia recruitment, and tau pathology.

Microglia: how do they inflame the brain in AD? (Hoon Ryu, KIST, Seoul, Korea)

This presentation was focused on novel insights on the major role of microglia and its non-cell-autonomous cycling of Aβ toxicity. It seems that microglial-activation is pre-programmed in homeostatic conditions or pre-clinical stages of AD, suggesting that microglia might play a useful role in normal conditions and then progress into dysfunctional cells in pathological conditions as if "friends become foes". On the other hand, activated microglia not only can trigger inflammation, but also cross-seed with neighboring neurons and astrocytes, sustaining, and accelerating diseased conditions. Based on these concepts, in this presentation, he was especially interested in tryptophan metabolism in microglia of AD. Tryptophan is a nutritionally essential amino acid that must be provided through dietary sources. Given the complexity of tryptophan metabolic pathways, diverse properties of tryptophan-derived metabolites have been linked to various pathophysiological states. He for the first time showed that inflammation-induced microglia activation produced endogenous toxin via an abnormal tryptophan metabolism in AD in his presentation.

Therapeutic strategy for AD based on immune-inflammatory biomarkers (Seung-Hyun Kim, Hanyang University, Seoul, Korea)

The presentation of Seung-Hyun Kim introduced platform development focusing on immune-inflammatory modulation as the diagnostic target for AD and related dementia such as ALS by adopting the importance of stratification and concept of personalized/precision medicine. To investigate this, his lab established and validated induced microglia-like cell model (iMGs) reflecting current on-going pathophysiology. He found that defective phagocytic function was clearly identified in iMGs from rapidly progressive ALS [ALS(R)-iMG]. In addition, he found previously unknown target related to defective microglial phagocytic function shown in ALS(R)-iMGs. Transcriptome analysis revealed that decreased X-mediated abnormal actin-polymerization perturbed phagocytic function in ALS(R)-iMG. In addition, X reduction in iMGs was related to abnormally exaggerated inflammatory response via NF-κB pathway. Because X activity could only be measured after a time-consuming process for generating iMGs, miRNA-A was identified as additional reliable biomarker related to X expression that could reflect clinical progression speed of ALS. Actually, plasma miRNA-A level was found to be correlated with each patient's current progression speed. Collectively, his data indicated that X and miRNA-A could be reliable biological markers for predicting the progression speed of ALS.

SESSION 3. VASCULAR CONTRIBUTION TO COGNITIVE IMPAIRMENT AND DEMENTIA

In this session, effects of vascular disease on cognitive function were discussed. Three speakers gave lectures on cognitive impairment in patients with diabetes mellitus (DM), the pathogenesis of VCI through a DEDEMAS cohort study, and the pathogenesis of post-stroke cognitive impairment (PSCI) from the perspective of brain connectivity.

Diabetes and dementia: disentangling vascular and degenerative aetiologies (Geert Jan Biessels, UMC Utrecht, Utrecht, the Netherlands)

Professor Biessel lectured from a broad perspective on how vascular risk factors could cause cognitive impairment. When type 1 diabetic patients were followed for 32 years, DCCT

and EDIC study results revealed that not only their immediate/delayed recall, but also their psychomotor/mental efficiency were decreased. These decreases were equivalent to about 9.4 years of aging.[10] In order to explain cognitive impairment in type 2 diabetic patients, he emphasized that approaching symptoms separately into "subtle change (diabetes-associated cognitive decrement)" and "impairment (MCI, dementia)" would be necessary. First, "subtle change" is a cognitive decline of about 0.3 to 0.5 standard deviations compared to the non-diabetes group. It was observed in all ages of type 1 and 2 DM patients to the extent that there was no significant impact on daily life. It was reported to be slow progressing.[11] Meta-analysis showed that the risk of dementia in diabetic patients was increased by about 1.43 times (risk ratio [RR], 1.43; 95% confidence interval [CI], 1.33–1.53). The risk was also increased for Alzheimer's dementia (RR, 1.43; 95% CI, 1.25–1.62) and vascular dementia (RR, 1.91; 95% CI, 1.61–2.52).[12,13] HbA1c was a risk factor for cognitive dysfunction in type 2 DM (T2DM) patients.[14] Amyloid pathology was not clearly associated with cognitive function in pathological studies, contrary to expectations. In the case of atrophy, lacunes, and WMH, a clear association of changes in the brain caused by T2DM has been revealed in several studies. However further studies are needed about effects of cerebral microbleeds, perivascular spaces, diffusion tensor images microstructures, and microinfarction on cognitive impairment.[15]

Pathophysiology of VCI: lessons from the DEDEMAS cohort (Marco Düring, University Hospital LMU Munich, Munich, Germany)

Professor Düring first discussed types and characteristics of various cognitive disorders over time after stroke. He explained concepts of strategic infarction dementia, multi-infarct dementia, early and delayed PSCI. He also introduced interesting research results using voxel-based lesion-symptom mapping on how strategic lesions in CADASIL patients could affect cognitive function and brain structures.[16,17] That is, a small lacune located in the anterior limb of the internal capsule can disconnect the anterior thalamic radiation and reduce the connected frontal cortical thickness, thereby causing cognitive decline including processing speed.[18] In addition, various research results based on DEDEMAS and DEMDAS cohorts were introduced. These cohorts included about 600 patients with cognitive test results, 3T magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), and functional MRI (fMRI). While explaining the concept of stroke-induced secondary neurodegeneration,[19] one study using DTI showed that the DTI index of the broad white matter pathway in the ipsilateral side of the lesion was significantly weakened compared to the white matter pathway in the contralateral hemisphere.[20] Results of the CIRCULAS and DEMDAS study showed that serum neurofilament light chain (NfL) level known to reflect structural damage increased as fast as 3–7 days after stroke onset. Other comorbidities affecting cognitive impairment after stroke were also discussed. It has been emphasized that small vessel disease is a more important determinant of cognitive decline than amyloid pathology.[21,22] Finally, the importance of early screening was emphasized by showing that an initial low MoCA score (<26 points) compared to an initial higher MoCA score (≥26 points) had a 5.30-fold higher risk of cognitive decline (odds ratio, 5.30; 95% CI, 2.75–10.22), a 5.03-fold higher risk for functional dependence (95% CI, 2.20–11.51), and a 7.24-fold higher risk of death (hazard ratio, 7.24; 95% CI, 1.99–26.35) at follow-up of 3 years.[23]

Brain connectivity and PSCI (Jae-Sung Lim, Asan Medical Center, Seoul, Korea)

Professor Lim explained from a network perspective why a cognitive dysfunction could occur after stroke. From the old phrenology concept to the recent lesion-symptom mapping method, he explained why the network perspective could be helpful when explaining

limitations of past research approaches. He then discussed the pathogenesis of cognitive impairment after stroke from various network perspectives ranging from the basic graph theory-based network indicators to the hierarchical structure. In particular, he introduced research results that a decrease in modularity due to local stroke lesions could lead to functional impairment. He also explained the mechanism to compensate for this decrease in segregation with an increase in integration. In addition, he emphasized that damage to the hub could cause widespread dysfunction in the entire brain. Subsequently, he discussed recent studies to classify functional structures in the brain into deep and superficial structures under Mesulam's concept of hierarchical structure and to predict cognitive function prognosis through this. In addition, he explained recent debate related to indirect lesion-network mapping, which estimated the effect on lesions in stroke patients using fMRI data obtained from normal people, considering that it would be difficult to directly evaluate stroke patients by fMRI. Finally, he emphasized that network changes caused by these lesions might vary depending on amyloid pathology, white matter hyperintensities, and blood-brain barrier disruption that might accompany each patient.

PLENARY SESSION 3. RECENT ADVANCEMENT IN BLOOD BASED BIOMARKERS FOR AD (RANDY BATEMAN, WASHINGTON UNIVERSITY, ST. LOUIS, MO, USA)

In autosomal dominant AD, amyloid deposition can be detected 15 years before the onset of cognitive symptoms, while cortical atrophy and hypometabolism can be detected 7 years before. There are three protein stages of AD. The tangle predominant stage correlates and progresses with cognitive symptoms. The plaque predominant stage begins 15 years before symptom onset. The pre-pathologic stage may be important for preventative treatment trials.

There are many advantages of blood tests for determining AD pathology. First, they can identify those with dementia who do not have AD. Second, they can identify cognitively normal people who are at risk of developing AD. Thus, they could be useful for prevention trials. Third, they are affordable, easily available, and noninvasive. Fourth, they can be used in research to study proteins in a quantitative manner.

Randall J. Bateman discussed recent advancements in blood-based biomarkers including Aβ42/40, tau, and NfL for detection of AD. Furthermore, they can potentially improve clinical trials by reducing the time of recruitment and cost. Of various blood-based biomarkers, plasma Aβ has been used in most studies. Levels of Aβ 42 in the plasma are consistently lower in AD patients like in cerebrospinal fluid (CSF) studies. There is a greater delineation according to APOE status. Plasma test for amyloid 42/40 detected amyloid plaques early than amyloid PET. Those with negative plasma amyloid were at zero risk of an abnormal PET scan over five years. Moreover, plasma Aβ42/40 status could predict future conversion to positive amyloid PET.[24] Currently, mass spectrometry-based methods seem to offer better precision than immunoassay for identifying individuals with early AD.[25] Plasma tau can also be detected in the blood. P-tau217 and P-tau181 are present in the plasma before the detection of neurofibrillary tangles. They could be detected almost as early as amyloid plaques. P-tau217 might be more useful than p-tau181 in the diagnostic work up of AD.[26] Microtubule binding region has strong correlations with clinical stage and tau PET SUVR, suggesting that it could be uses as an indicator of tau tangles.[27] Bateman also discussed his ongoing research on

isoforms of NfL in AD and showed that the detection of NfL using mass spectrometry and ligands targeting c-terminal region appeared to be more specific for AD.

SESSION 4. NEUROPSYCHOLOGY: WHERE IS IT HEADED FOR?

In the neuropsychology session, three speakers presented their research related to the clinical and academic future of neuropsychology.

Reliability, validity, and user-experience of computerized neuropsychological instruments to detect cognitive impairment in older adults (Nicole A. Kochan, UNSW Sydney, Kensington, Australia)

Dr. Kochan from UNSW Sydney, Australia presented her research about the test-retest reliability, concurrent validity, and the overall test-taking experience of four computerized batteries (the CANTAB, Cogstate, Cambridge Brain Sciences, and NIH toolbox) completed by community dwelling older adults in the CogSCAN Study and Maintain Your Brain Validation Study. Test-retest reliabilities of these measures were variable, with composite scores having better reliability. Furthermore, relationships between sets of computerized and paper-and-pencil tests were strong. Although participants' ratings about user-experience of these computerized testing indicated that these tests were mostly easy to understand, enjoyable, and interesting, anxiety about test performance and difficulties of concentrating on computerized testing could be some issues for many individuals regardless of the setting.

Individual difference and lifestyle factors affecting brain aging and beta-amyloid deposition and cognition in preclinical AD (Hwamee Oh, Brown University, Providence, RI, USA)

Dr. Oh from Brown University, USA introduced the concept of individual difference in risk and resilience for Alzheimer's pathology. The degree of brain aging is related to the performance of older adults. However, the relationship between brain aging and cognitive function can be affected by individual difference and lifestyle factors. Individual difference and lifestyle factors include biological, psychological, and environmental factors potentially modifiable or non-modifiable. She presented several brain imaging studies, showing that interactions among APOE ε4 genotypes, increased glucose metabolism, regional brain activity, higher functional connectivity, and hippocampal redundancy played a role of resilience to Alzheimer pathology or brain aging. She also suggested that with lifestyle intervention such as US POINTER imaging study and longitudinal study over 60 years, researchers will be able to identify individual and lifestyle factors that play a critical role at different time points across lifespan and neural mechanisms underlying the risk and resilience to the development of Alzheimer pathologies.

Cognitive composite scores are sensitive for determining subtle cognitive decline in preclinical AD (Juhee Chin, Samsung Medical Center, Seoul, Korea)

The third speaker Dr. Chin from Samsung Medical Center, Korea presented cognitive composite scores to detect subtle cognitive decline in preclinical AD. Recent research on AD has shifted in focus from the clinical stage to the preclinical stage for early detection of disease. With this research trend, it is critical to identify subtle cognitive decline in the preclinical stage of AD. It is also important to develop a single effective cognitive composite score for use as a clinical outcome measure in secondary prevention. In her presentation,

she explained a few well-known cognitive composite scores (such as Preclinical Alzheimer Cognitive Composite) and 2 cognitive composite scores used for detecting subtle cognitive decline in cognitively normal older adults with amyloid deposition in Korea: the Preclinical Amyloid Sensitive Composite (PASC) and the Longitudinal Amyloid Cognitive Composite in Preclinical AD (LACPA). She suggested that these scores might be used as representative scores for global cognitive function and as outcome measures in preclinical AD drug trials.

SESSION 5. BLOOD-BASED BIOMARKERS FOR AD

These days, many researchers are trying to find blood-based biomarkers for AD that can be used for diagnosis and treatment monitoring as well as for understanding the pathophysiology of AD. Topics in this session dealt with not only blood biomarkers such as amyloid and phosphorylated tau, but also oligomerization tendency of Aβ and biomarkers for liver enzymes and bile acids.

Novel blood biomarkers in AD: from metabolic pathways to biomarkers (Kwangsik T. Nho, Indiana University School of Medicine, Indianapolis, IN, USA)

Dr. Nho presented recent studies using the AD Metabolomics Consortium (ADMC) data which identified the role of the gut microbiome, liver enzymes, and bile acids in AD progression, cognitive decline, and brain structural and functional biomarkers for AD, highlighting the crosstalk between peripheral and central compartments. He pointed out that understanding the association between circulating serum-based metabolites/lipids and A/T/N biomarkers of AD could shed light on the mechanisms underlying the association between biochemical perturbations and AD risk and lead to the identification of novel blood-based biomarkers.

Aβ oligomerization in blood of AD (Young Chul Youn, Chung-Ang University, Seoul, Korea)

In his presentation, Dr. Youn dealt with Multimer Detection System-Oligomeric Aβ (MDS-OAβ) that could measure oligomerization tendencies in blood. Increased MDS-OAβ in plasma was significantly associated with the diagnosis of AD, brain volume reduction in the temporoparietal area, and increased positivity of amyloid PET. He suggested that MDS-OAβ could be one of AD blood biomarkers.

Blood-based biomarkers for AD: becoming a reality (Charlotte E. Teunissen, VU University Medical Center, Amsterdam, the Netherlands)

Dr. Teunissen presented that blood levels of Aβ1-42/Aβ1-40 and phosphorylated tau were associated with the diagnosis of AD as well as CSF and PET (amyloid/tau) levels of corresponding biomarkers. Furthermore, other neurodegenerative blood-based biomarkers such as neurofilament light and more recently glial fibrillary acidic protein also appeared to provide information on disease progression and potential for monitoring treatment effects. Although blood-based biomarkers for AD seemed unattainable for many years, her recent works have shown that they could become a reality.

PLENARY SESSION 4. CAN WE PREVENT DEMENTIA? (GILL LIVINGSTON, UCL, LONDON, ENGLAND)

First, Dr. Gill Livingston explained why we could consider dementia preventable. Based on recent study results, dementia incidence decreased by 25% during the last 20 years in US

& Europe while it was stable or increased in other countries including Japan, Korea, Hong Kong, and Brazil. Such differences between countries could be explained by increased cognitive reserve and reduction in brain damage in areas with higher income and more educated people. It also suggests that dementia might be evitable.

Second, she explained about modifiable risk factors of dementia. In 2020, previously reported nine modifiable risk factors were revised to 12 risk factors (three risk factors including traumatic brain injury [TBI], air pollution, and alcohol were added). According to the article, there are 12 modifiable risk factors. Controlling these factors might prevent or delay up to 40% of dementias.

Each modifiable risk factor and previous study results regarding risk factors were explained. First, hearing loss associated with temporal lobe atrophy might decrease dementia risk. Second, education is important for cognitive reserve. People with cognitively stimulating jobs can decrease 20% risk reduction. Third, smoking can lead to cardiovascular pathology because cigarette smoke contains neurotoxins. Gil stated that passive smoking was also a risk factor. High social contact is associated with late-life cognitive function. Alcohol drinking for more than 21 units (14 Korean units) was a risk factor of dementia. Both severity and number of TBI were risk factors of dementia. Regarding air pollution, exposure to PM2.5, NO2, and CO could increase all dementia risk. Persistent midlife hypertension increased the risk of late life dementia. Body mass index over 30 might increase dementia risk. Depression is associated with dementia incidence, with a variety of possible psychological or physiological mechanisms. Whether antidepressant treatment could mitigate dementia risk remains unclarified. Regarding physical inactivity, although studies on physical activity are complex because patterns, disease severity, and types of physical exercise could vary. Previous study results have consistently suggested a relationship between physical activity (exercise) and dementia risk reduction. Overall type 2 diabetes was a clear risk factor for the development of future dementia. However, whether any particular medication could ameliorate this risk of dementia is unclear. Intensive diabetic control does not decrease the risk of dementia.

She stated whether dementia risks were the same for everyone. Because most cohort studies were primarily based on white participants in high income countries, risks could vary between countries. Interventions should be individualized, considering the person as a whole. Hence, further studies is needed to confirm the study results and assess individualized dementia risk. She also presented previous clinical trials for effective and practical interventions to decrease dementia risks. She explained about the FINGER trial and the Superbrain trial in Korea.

SESSION 6. PUBLIC HEALTH AND EPIDEMIOLOGY

Due to the lack of effective pharmacological treatments to recover cognitive status in patients with dementia, the importance of preventive strategies in public health has been highlighted. In 2019, the World Health Organization (WHO) introduced the first guidelines for the risk reduction of cognitive decline[28] including 12 modifiable risk or protective factors (physical activity, tobacco consumption/cessation, nutrition, alcohol use disorders, cognitive activity, social activity, overweight/obesity, hypertension, DM, dyslipidemia, depression, and hearing loss) based on recent systematic review[29] and guidelines.[30] In this session, three presenters

covered recent progress and challenges in the field of research related to dementia prevention or successful aging.

The SuperAgers' brain (Geon Ha Kim, Ewha Womans University, Seoul, Korea)

Professor Kim introduced the concept of superagers referring to older adults whose cognitive abilities were comparable to middle aged people or young adults. Therefore, previous studies have suggested that SuperAgers might have some resilience against age-related decline. Professor Kim presented neuropsychological and neuroimaging characteristics in Korean SuperAgers. SuperAgers demonstrated not only better performances in memory, but also better performances in attention, visuospatial and frontal executive functions compared to typical agers. In addition, SuperAgers showed higher functional connectivity than typical agers in the default mode, central executive, and salience network as well as multiple demanding networks, all of which are known to be involved in the cognitive process.

Multidomain lifestyle intervention: progress & future (Seong Hye Choi, Department of Neurology, Inha University School of Medicine, Incheon, Korea)

Professor Choi presented results of the SoUth Korean study to PrEvent cognitive impaiRment and protect BRAIN health through lifestyle intervention in at-risk elderly people (SUPERBRAIN), part of the World-Wide FINGERS (WW-FINGERS). The SUPERBRAIN program consisted of a facility-based (FMI) program and a home-based multi-domain intervention (HMI) program, including management of metabolic and vascular risk factors, cognitive training and social activity, physical exercise, nutritional guidance, and motivational enhancement programs for six months. From eight centers in Korea, A total of 152 older adults aged 60–79 without dementia were recruited for this study. They had at least one modifiable dementia risk factor. They were randomly allocated to FMI, HMI, and control groups at a 1:1:1 ratio. Professor Choi showed that both FMI and HMI programs of the SUPERBRAIN improved cognitive function of at-risk older people in Korea. In addition, Professor Choi discussed the necessity of developing non-face to face intervention programs for patients with cognitive impairment, especially during this challenging COVID-19 pandemic.

Japan's challenge for anti-dementia measures: coexistence and prevention (Hidenori Arai, National Center for Geriatrics and Gerontology, Obu, Japan)

Professor Hidenori introduced National Dementia Strategy in Japan, which focused on the establishment of dementia-friendly society (coexistence) and prevention of dementia. Professor Hidenori presented "New Orange Plan" as a comprehensive strategy for coexistence to create a community where people with dementia could live with dignity in a peasant and familiar environment. As for the prevention of dementia, Professor Hidenori emphasized the importance of multidomain intervention programs and presented an ongoing, multicenter, randomized controlled trial of multidomain intervention among patients with mild cognitive impairment in Japan (J-MINT), a part of WW-FINGERS. The J-MINT intervention includes management of vascular risk factors, group-based physical exercise program, increased physical activity, nutritional counselling, and cognitive training using BrainHQ. Cognitive function and other measures including blood biomarkers for Aβ deposition and brain MRI are assessed at baseline, 6, 12, and 18 months.

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