THE CROATIAN ACADEMY OF SCIENCES AND ARTS
The Department of Biomedical Sciences in Rijeka
THE CLINICAL HOSPITAL CENTER RIJEKA
UNIVERSITY OF RIJEKA - FACULTY OF MEDICINE
THE CROATIAN NEUROLOGICAL SOCIETY
THE CROATIAN MEDICAL ASSOCIATION – Branch office Rijeka

8th RIJEKA FORUM ON NEURODEGENERATIVE DISEASES

THE REGULATION OF GENE EXPRESSION IN NEUROLOGICAL DISEASE AND NEUROIMMUNOLOGY

ACADEMIA SCIENTIARUM ET ARTIUM CROATICA
MDCCCLXI

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NEURODEG

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SOCIETÀ ITALIANA PARKINSON E DISORDINI DEL MOVIMENTO LIMPE-DISMOV ETS

Rijeka, September 16-17, 2024
08:30 am
University Campus Rijeka, Faculty of Civil Engineering
Lecture halls G-003 and G-004, Radmile Matejčić 3, Rijeka

Organizers

THE CROATIAN ACADEMY OF SCIENCES AND ARTS
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Scientific Committee

Stipan Jonjić, Vladimira Vuletić, Nenad Bogdanović, John Hardy,
Alen Ružić, Zdravka Poljaković

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Registration: online via registration form

Free admission for registrations

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PROGRAM
OPENING
(8:30-9:00)

Introduction

Stipan Jonjić, M.D., PhD, Professor, Academician, Head of the Department of Biomedical Sciences in Rijeka, Croatian Academy of Sciences and Arts, Rijeka, Croatia

Vladimira Vuletić, M.D., PhD, Professor, Faculty of Medicine, University of Rijeka, Rijeka, Croatia

Welcome address

Zdravka Poljaković, M.D., PhD, Professor, President of the Croatian Neurological Society, Medical Faculty, University of Zagreb, Zagreb, Croatia

Alen Ružić, M.D., PhD, Professor, Director, Clinical Hospital Center, Rijeka, Croatia

Goran Hauser, M.D., PhD, Professor, Dean, Faculty of Medicine, University of Rijeka, Rijeka, Croatia

Snježana Prijić Samaržija, PhD, Professor, Rector, University of Rijeka, Rijeka, Croatia

1st day – September 16th, 2024

PROGRAM

9,00 – 12,00 h

I. ALZHEIMER'S DISEASE UPDATES

Chairmen: Nenad Bogdanovć **and Elka Stefanova**

John Hardy, M.D., PhD, Professor, Institute of Neurology, University College London, London, UK
Neurodegenerative diseases: anti-amyloid therapies for Alzheimer's disease are the first faltering steps towards mechanistic therapy

Nenad Bogdanović, M.D., PhD, Professor, Karolinska Institute, Stockholm, Sweden
Alzheimer's disease mismatch: LATE and PART

Catherine Mummery, M.D., PhD, Professor, National Hospital for Neurology and Neurosurgery, London, UK
Emerging therapies in Alzheimer's disease: translating genetics into clinical impact

Silva Katušić, PhD, Professor, Institut Ruđer Bošković, Zagreb, Croatia
Which comes first: neuroinflammation or neurodegeneration – the case of juvenile Alzheimer's disease

Amos D. Korczyn, M.D., PhD, Professor Emeritus, CONy President, Tel Aviv University, Tel Aviv, Israel
Is Alzheimer's disease a disease?

Elka Stefanova, M.D., PhD, Professor, School of Medicine, University of Belgrade, Belgrade, Serbia
The role of Fluid biomarkers in the diagnosis of Alzheimer's disease continuum

Discussion: 12:00 – 12:15

Break for refreshment: 12:15 – 12:30

12,30 – 14,30 h

II. ALPE ADRIA SECTION AND MOVEMENT DISORDERS (1st PART)

Chairmen: Vladimira Vuletić and Maja Trošt

Elena Moro, M.D., PhD, Centre Grenoble University Hospital Center and Grenoble Alpes University, Grenoble, France
What DBS will be able to do in the next 5 years?

Kailash Bhatia, M.D., PhD, Professor, Institute of Neurology, University College London, London, UK
A new gene for Parkinson's and new predictive biomarker

Angelo Antonini, M.D.,PhD, Professor, Neurology Clinic Padua and University of Padua, Padua, Italy
Disease modifying strategies

Michele Tinazzi, M.D.,PhD, Professor, University of Verona, Verona, Italy
Axial Postural abnormalities in PD

Discussion: 14:30 – 14:45

Lunch break and Flesh presentation of young researchers: 14:45– 15:45

Valentino Rački, M.D., PhD, Clinical Hospital Center Rijeka, Rijeka, Croatia
A new form of MS treatment (15:30 – 15:45)

15,45 – 17,45 h

III. MULTIPLE SCLEROSIS AND NEUROIMMUNOLOGY

Chairmen: Borut Peterlin and David Bonifačić

Celia Oreja-Guevara, MD, PhD, University Hospital San Carlos and Complutense University of Madrid, Madrid, Spain
Are imaging (MRI) and biomarkers useful tools for disease monitoring in NMOSD?

Borut Peterlin, M.D., PhD, Professor, University Medical Center Ljubljana, Ljubljana, Slovenia
Genetics in Multiple sclerosis

Gregor Brecl Jakob, M.D., PhD, Assistant Professor, University Medical Center Ljubljana, Ljubljana, Slovenia
Clinical, MRI and laboratory correlates of degeneration/progression in MS

David Bonifačić, M.D., PhD, Assistant Professor, Clinical Hospital Center Rijeka, Rijeka, Croatia
Epstein–Barr virus and multiple sclerosis: moving from questions of association to questions of mechanismAtypical atypical parkinsonism: the catalogue of genetic and immune-mediated mimics

Discussion: 17:45 – 18:00

2nd day – September 17th, 2024

9,00 – 11,00 h

IV. ALPE ADRIA SECTION AND MOVEMENT DISORDER TREATMENTS (2nd PART)

Chairmen: Vladimira Vuletić and Maja Trošt

Aleksandra Tomić, M.D., PhD, School of Medicine, University of Belgrade, Belgrade, Serbia
Genetic landscape of complex dystonia syndromes

Norbert Kovacs, M.D., PhD, Professor, Department of Neurology, University of Pecs, Pecs, Hungary
Functional symptoms in Parkinson's disease patients treated with device-aided therapies

Maja Trošt, M.D., PhD, Professor, University Medical Centre Ljubljana, Ljubljana, Slovenia
Long term efficacy of device aided therapies in advanced parkinson's disease and reasons for switching and combinig them

Iva Stanković, M.D., PhD, Assistant Professor, School of Medicine, University of Belgrade, Belgrade, Serbia
An update on multiple system atrophy

Milica Ječmenica Lukić, M.D., PhD, Assistant Professor, Faculty of Medicine, University of Belgrade, Belgrade, Serbia
Atypical atypical parkinsonism: the catalogue of genetic and immune-mediated mimics

Discussion: 11:05 – 11:15

Break for refreshment: 11:15 – 11:30

11,30 – 14,10 h

V. NEURODEGENERATIVE DISORDERS UPDATES

Chairmen: Patrick Küry and Zvezdan Pirtošek

Vida Demarin, M.D., PhD, Professor, Academician, Secretary of the Department of Medical Sciences of the Croatian Academy of Sciences and Arts, President of International Institute for Brain Health, Zagreb, Croatia
The role of stress in neurodegenerative diseases

Patrick Küry, M.D., PhD, Professor, Medical Faculty, Heinrich-Hein University of Düsseldorf, Düsseldorf, Germany
Functional assessment of endogenous retrovirus mediated neurodegeneration via transcriptome analysis

Paolo Manganotti, M.D., PhD, Professor, Cattinara University Hospital ASUGI and University of Trieste, Trieste, Italy
Non invasive brain stimulation in degenerative disorders

Dinko Mitrečić, M.D., PhD, Professor, Croatian Institute for Brain Research, Zagreb, Croatia
How do stem cells change expression of genes involved in cell death and autophagy in the neural tissue affected by hypoxia?

Zvezdan Pirtošek, M.D., PhD, Professor, University Medical Center Ljubljana, Ljubljana, Slovenia
Can lamarckism explain cognitive evolution in humans?

Ivana Munitić, M.D., PhD, Professor, Faculty of Biotechnology and Drug research, University of Rijeka, Croatia
Analysis of optineurin variants in neurodegenerative diseases

Gabriela Novotni, M.D., PhD, Professor, University Clinic of Neurology, Medical Faculty, University "Ss Cyril and Methodius", Skopje, North Macedonia
What is in a name and what is in the brain - a few short dementia stories on genotype/phenotype correlation and protein aggregation

Jason Cannon, PhD, Professor, Purdue University, West Lafayette, SAD
Parkinson's disease risk and mechanisms from military relevant organophosphate exposures

Fran Borovečki, M.D., PhD, Professor, University Hospital Centre Zagreb, Zagreb, Croatia
Immunogenetics of Parkinson's disease-a single cell sequencing approach

Discussion: 14:10 – 14:25

Lunch and Flesh presentation of posters of young researchers: 14:25-15:25

Ante Tolić, M.D. Clinical Hospital Center Rijeka, Rijeka, Croatia
Non-specific signs in LOPD patients (15:05 – 15:25)

15,25 – 17,15 h

VI. PARKINSON'S DISEASE UPDATES ON GENETICS AND NEUROIMMUNOLOGY

Chairmen: Slavica Kovačić and Vladimira Vuletić

Nataša Klepac, M.D., PhD, Professor, University Hospital Centre Zagreb, Zagreb, Croatia
How can non-pharmacological interventions support a person with cognitive impairment?

Slavica Kovačić, M.D., PhD, Assistant Professor, Clinical Hospital Center Rijeka, Rijeka, Croatia
Kristijan Stojšić, mag. phys. Clinical Hospital Center Rijeka, Rijeka, Croatia
Free-water imaging in Parkinson's disease

Dejan Georgiev, M.D., PhD, Professor, University Medical Centre Ljubljana, Ljubljana, Slovenia
Genetic testing before deep brain stimulation for movement disorders: is it really needed?

Vladimira Vuletić, M.D., PhD, Professor, Clinical Hospital Center Rijeka and Faculty of Medicine, University of Rijeka, Rijeka, Croatia
Microbiota and neurodegenerative disorders

17,10 h

VII. CLOSING REMARKS

Chairman: Vladimira Vuletić

ABSTRACTS

Neurodegenerative diseases: anti-amyloid therapies for Alzheimer's disease are the first faltering steps towards mechanistic therapy

John Hardy
Institute of Neurology and Dementia Research Institute, UCL, London, UK

Ab was isolated and sequenced from the amyloid angiopathy of Alzheimer's disease in 1984 and from plaque cores in 1985. By oligonucleotide hybridisation the APP gene was cloned and localised to chromosome 21 in 1987. After a false start, APP mutations were identified in Dutch amyloid angiopathy in 1990 and in a minority of early onset Alzheimer families in 1990. In other families with early onset Alzheimer's disease, mutations were described in the presenilin genes in 1995 and the effects of both APP and presenilin mutations on APP processing was described in 1996. Mice with APP and mice with APP and presenilin mutations which deposited plaques but not tangles were made in 1994-1998. MAPT mutations were found in tangle only dementias in 1998 and these mutations allowed mice with tangles to be produced in 2000. Crossing these tangle mice with the plaque mice potentiated tangle formation but did not alter plaque production showing tangles and cell loss were downstream or amyloid in the pathogenic cascade. This sequence of findings largely made from the analysis of early onset mendelian disease is what has underpinned the amyloid hypothesis. More recently, genetic analysis of the much more prevalent late onset disease has identified many loci most of which are involved in microglial Ab clearance.

This background justified the three major therapeutic approaches to Alzheimer's disease based on either reducing Ab production of facilitating Ab clearance.

Ab is produced by the sequential cleavage of APP by b-secretase at the N terminal of Ab and g-secretase at the C terminal of Ab. With this background, there have been three major therapeutic targets: b-secretase inhibition, g-secretase inhibition/modulation and amyloid removal by antibody. Both b- and g- secretase inhibition failed in clinical trials possibly because both enzymes have many other substrates besides APP or because the build up of C-terminal stubs of APP was neurotoxic. Attempts at g-secretase modulation (altering the cleavage site of the enzyme) continue. The major developments have come from the use of antibodies to either prevent amyloid build up or to facilitate amyloid removal.

The first hint that antibodies to Ab might be a useful therapeutic strategy came from the experimental treatment of transgenic mice in 1999. However, while this first antibody and some of the other early antibodies prevented amyloid build up, they did not cause amyloid removal except where there was blood brain barrier damage. These antibodies failed in clinical trials. After these failures and the failures of b- and g- secretase inhibitors there was concern and disagreement in the research community about whether amyloid therapies were worth further pursuing. However, more recently, antibodies which caused amyloid removal, aducanemab (controversially), lecanemab and

dononamab have all caused amyloid removal, and have led to modest clinical benefit and have therefore received some regulatory approval. All though, cause blood vessel inflammation (ARIA) as the antibodies hit the amyloid angiopathy.
In my talk I will review these issues and discuss the genetic and pharmacologic attempts to both improve anti-amyloid therapies and to decrease their side effects.

Alzheimer's Disease mismatch: LATE and PART

Nenad Bogdanović
Karolinska Institute, Stockholm, Sweden

One of the key morphological features of the aging brain is the accumulation of pathological proteins in the limbic region, particularly in the hippocampus. In individuals without evidence of amyloid, higher levels of tau or TDP-43 in the medial temporal lobe are associated with increasing age. Among the subregions of the temporal lobe, episodic memory is most strongly linked to the entorhinal cortex. Our findings align with neuropathological studies and further suggest that protein pathology in the entorhinal region contributes to memory decline in older adults, even in the absence of amyloid.
A significant subset of patients over 65 years old, particularly those over 80, who exhibit normal cognition or mild cognitive impairment (MCI), are amyloid-negative but show evidence of neurodegeneration through cerebrospinal fluid (CSF) biomarkers, MRI biomarkers, and neuropsychological testing. These patients may be misdiagnosed with Alzheimer's disease (AD) and receive inappropriate treatment if biomarker analysis is not conducted, as their clinical presentation can mimic early AD. The concept of suspected non-Alzheimer's disease pathophysiology (SNAP) has been introduced. SNAP is present in approximately 23% of clinically normal individuals over 65 and in about 25% of those with MCI. The APOE4 allele is underrepresented in individuals with SNAP compared to those who are amyloid-positive, further supporting the absence of amyloid in these early stages. Individuals with SNAP who still have normal cognition or MCI experience worsening clinical and cognitive outcomes later in life.
SNAP was initially described in a study that examined the National Institute on Aging–Alzheimer's Association (NIA–AA) criteria for preclinical AD. Currently, the term SNAP is less commonly used and is being replaced by more specific entities such as LATE (Limbic-predominant Age-related TDP-43 Encephalopathy) and PART (Primary Age-Related Tauopathy).
The patterns of atrophy and hypometabolism seen in non-AD conditions often overlap with those observed in AD, particularly in the medial temporal lobe. Hippocampal atrophy is not exclusive to AD; it is also observed in conditions like hippocampal sclerosis, TDP-43 pathology (LATE), anoxic–ischemic injury, and PART, which can be presented as Argyrophilic grain disease and/or Tangle-only dementia. Similarly, glucose hypometabolism in non-AD conditions can mimic that of AD, particularly with a temporoparietal pattern of decreased glucose uptake. This AD-like hypometabolism in posterior association areas can be explained by the fact that these regions are highly connected, both structurally and functionally, to the medial temporal lobe.
LATE and PART are almost universally detectable at autopsy in elderly individuals. However, these pathological processes are difficult to identify before death, although

certain clinical features and a newly established LATE clinical criteria could suggest non-AD features. This concept is still evolving, but significant progress has been made in understanding the differential diagnosis of dementia in individuals over 80 years old who suffer from PART or LATE. It is crucial for practitioners to be aware of these common pathological changes (PART, and LATE) because the final diagnosis and treatment may differ from those for AD. Cognitive impairment in these conditions is often mild and long-lasting while patients can maintain daily activity longer than in AD. MRI can reveal asymmetric hippocampal atrophy characteristic of both AD and LATE/PART. Unlike typical AD, where hippocampal atrophy does not show an clear anterior-posterior gradient, atrophy in definitive LATE/PART shows a predominance in the anterior region and on the left side. This distinction is clinically important because the anterior and posterior hippocampus are involved in different aspects of episodic memory, with the posterior hippocampus associated with retrieval and the anterior with encoding of the novel information. The absence of posterior hippocampal degeneration can be assessed neuropsychologically, potentially indicating a different neurodegenerative pathway and thus a clinical difference between AD and LATE/PART.

Similarly, in semantic dementia, involvement of the anterior hippocampus is the MRI hallmark, and this condition is characterized by relatively spared episodic memory. While LATE/PART and semantic dementia may share some MRI features, the overall clinical and neuropsychological profiles, age of onset, and specific patterns of gyrus degeneration clearly distinguish these neurodegenerative entities. Furthermore, LATE/PART differs from AD by the low frequency of the APOE4 allele. The frequency of APOE4 in AD is three to four times higher than in LATE/PART. APOE4 has been linked to the accumulation of beta-amyloid, which is why LATE/PART has less or no amyloid pathology. Consequently, LATE/PART has cognitive outcomes that should be considered in the context of emerging therapies targeting TDP-43 or tau in age-associated neurodegenerative diseases.

Neurobiologically, the hippocampal formation is particularly vulnerable to tau and TDP-43, which are the morphological substrates of age-related episodic memory loss and late dementia in old age. In summary, the clinical features of LATE/PART are distinct from those of AD, and recognizing this distinction is critically important for the clinical management of patients with cognitive impairment and for public health care planning.

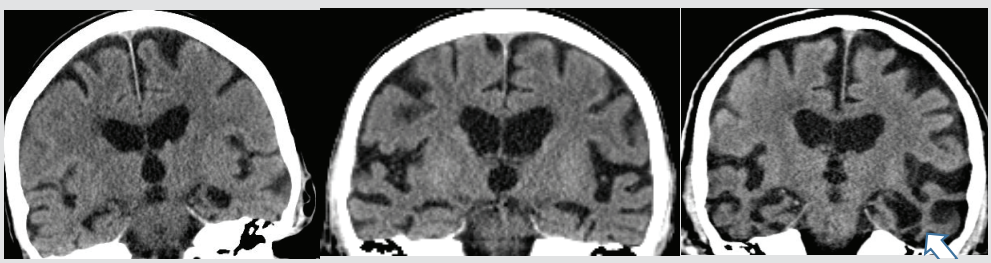

Figure 1: CT coronary images at the level of the anterior hippocampus in patients with PART (A), late-onset Alzheimer's Disease (B), and Primary Progressive Fluent Aphasia – Semantic Dementia (C). Note the predominant left > right anterior hippocampal atrophy in all three patients, which should not be attributed solely to Alzheimer's Disease.

- Patient A (PART): An 85-year-old with an MMSE score of 23/30, APOE 2/3 genotype, and normal CSF biomarkers. The patient exhibits predominantly amnestic cognitive impairments and mild dementia.
- Patient B (late-onset AD): A 84-year-old patient with APOE 4/3 genotype, CSF biomarkers indicative of AD, and an MMSE score of 20/30. The patient presents with primary amnestic cognitive impairment and mild dementia. In addition to medial temporal lobe (MTL) atrophy, mild to moderate cortical atrophy is observed.
- Patient C (Semantic Dementia): A 75-year-old patient with moderately advanced Semantic Dementia, characterized by severe atrophy of the left MTL and temporal pole, extending to the contralateral temporal lobe and left frontal cortex. The patient has normal CSF biomarkers, an APOE 3/2 genotype, and an MMSE score of 19/30. Clinical presentation includes progressive fluent aphasia as part of frontotemporal lobar degeneration (FTLD). Early identification of pathognomonic atrophy of the fusiform gyrus (white arrow) can indicate Semantic Dementia in its very early stages.

Without the use of biomarkers and careful image analysis, patients A and C are often misdiagnosed with Alzheimer's Disease, leading to significant consequences in the post-diagnosis management of these phenotypes.

Emerging therapies in Alzheimer's disease: translating genetics into clinical impact

Catherine Mummery
National Hospital for Neurology and Neurosurgery, London, UK

The world is changing. We have the first treatments to alter the course of Alzheimer's disease and are at the beginning of a journey towards AD being a chronic, manageable disorder. In my talk, I will describe the role genetics has played in this journey, guiding our focus in finding targets and treatments in AD, informing us on how we might best influence the course of disease and helping us develop novel therapies that promise to radically alter our ability to treat. I will give some examples of groundbreaking genetic modulation therapies along the way, and on why this is so important for our patients and families.

Which comes first: neuroinflammation or neurodegeneration – the case of juvenille Alzheimer's disease

Silva Katušić
Ruđer Bošković Institute, Zagreb, Croatia

Niemann-Pick type C disease (NPC) is a rare, inherited, neurodegenerative disorder caused by mutations in the NPC1 or NPC2 genes that code for intracellular cholesterol transport proteins. NPC is also called juvenile Alzheimer's disease (AD) as it shows several key features of AD including increased levels of the amyloid-β peptides (Aβ), accumulation of hyperphosphorylated tau and neurofibrillary tangles, apolipoprotein E isoform ε4 involvement in the disease progression, dysfunction of the endolysoso-

mal pathway, neurodegeneration and profound neuroinflammation (activation of astrocytes and microglia). The molecular mechanism of neurodegeneration in NPC - first manifested by the loss of Purkinje neurons following the loss of cortical neurons - is currently unknown. Although peripheral organs such as liver and spleen are also affected by the disease, expression of NPC1 restricted to central nervous system rescues not only neurodegeneration, but also lethality of NPC1-mice. Therefore, molecular understanding of NPC pathology in the brain is crucial for the design of future therapeutic options. The restoration of NPC1 in neurons only, does not fully rescue the phenotype and lethality, indicating that NPC1 is functionally important in other brain cells as well. Indeed, NPC1 is ubiquitously expressed throughout the brain with particularly high expression in microglia and oligodendrocytes. Current treatments (using miglustat or methyl-β-cyclodextrin) can alleviate symptoms somewhat, but cannot sustainably halt progression of the disease. As no effective therapy is available for NPC, most of the patients die between 10-25 years of age. It is therefore of high priority to develop new therapeutic options to attenuate this devastating disease. The goal of our work is to elucidate early changes that drive neurodegeneration and/or neuroinflammation in NPC disease and to better understand the interrelationship between these two processes.
It has been generally assumed that in neurodegenerative diseases neuroinflammation is a bystander of neuronal loss. However, our recent findings in NPC1 mice and in NPC patients' blood-derived macrophages, suggest a possible causative rather than consequential role of neuroinflammation in neuropathology. We have recently demonstrated for the first time that NPC microglia proteome changes precede neuronal loss and act in cell autonomous manner, thus contributing to neuropathology. Importantly, we showed that lipid accumulation in NPC1-mouse microglia is a consequence of impaired lipid trafficking with a striking accumulation of multivesicular bodies. The late endosomal/exosomal marker CD63 was the most significantly changed protein at presymptomatic stage (at postnatal day 7 - P7), suggesting that defects within endosomal/lysosomal trafficking and sorting may be among the earliest pathological alterations in NPC microglia. Together with early activation of microglia (CD68), our preliminary results suggest similar early activation of astrocytes (GFAP) in P7 old NPC1 mouse brains as well. In sum, we showed that neuroinflammation precedes neurodegeneration in NPC disease, suggesting that neuroinflammation may have causative rather than consequential role in neuropathology of NPC. Thus, anti-inflammatory therapies may be considered as early treatment strategies against NPC disease and, potentially, against other neurodegenerative disorders with strong neuroinflammation.

Is Alzheimer's disease a disease?

Amos D Korczyn
Tel Aviv University, Tel Aviv, Israel

Dementia, a prevalent condition among older individuals, has profound societal implications. Extensive research has resulted in no cure for what is perceived as the most common dementing illness: Alzheimer disease (AD). AD is defined by specific brain abnormalities — amyloid-β plaques and tau protein neurofibrillary tangles — that are proposed to actively influence the neurodegenerative process. However, conclusive evidence of amyloid-β toxicity is lacking, the mechanisms leading to the accumulation

of plaques and tangles are unknown, and removing amyloid-β has not halted neurodegeneration. So, the question remains, are we making progress towards a solution? The complexity of AD is underscored by numerous genetic and environmental risk factors, and diverse clinical presentations, suggesting that AD is more akin to a syndrome than to a traditional disease, with its pathological manifestation representing a convergence of pathogenic pathways. Therefore, a solution requires a multifaceted approach over a single 'silver bullet'. Improved recognition and classification of conditions that converge in plaques and tangle accumulation and their treatment requires the use of multiple strategies simultaneously.

The role of fluid biomarkers in the diagnosis of Alzheimer's disease continum

Elka Stefanova[1,2]
[1]University of Belgrade, Faculty of Medicine, Belgrade, Serbia
[2]University Clinical Centre of Serbia, Belgrade, Serbia

Rapid progress in the determination of classic cerebrospinal fluid (CSF) biomarkers has contributed to the understanding of the dynamic links between the pathophysiological processes associated with Alzheimer's disease (AD). Beta amyloid Aβ (A), tau (T) which includes Phospho tau (F-Tau) and Total tau (T-tau) are recognized as classic CSF biomarkers in AD. Recently, a less invasive and more accessible procedure is the determination of these basic but also other new specific biomarkers from blood/plasma. More recently, it has been shown that increased reactivity of astrocytes plays a role in the association of Ab with early tau phosphorylation in preclinical AB, and this is indicated by elevated glial fibrillary acidophilic protein (GFAP) in plasma.
We will present a quite-long experience (from 2006 -2023) of determining classic CSF biomarkers in various dementias from the Center for Memory Disorders at the Neurology Clinic UKCS Belgrade, where (n=1240) patients were examined. We will also present the latest pilot experience with the blood biomarkers Aβ42/Aβ40, F-Tau, and the findings of astrocytic and microglial activation in persons with mild cognitive impairment, or in patients who already have the confirmed presence of beta amyloid (category A) using PET methodology with an amyloid marker. While the difference in plasma Aβ42/Aβ40 ratio between Aβ-positive and negative individuals is quite modest (14-20% reduction), the increase in plasma F-Tau concentration is about 3-fold, giving a very very high diagnostic accuracy for AD (85-95%). Plasmin F-Tau could serve as a good screening test with the inclusion of GFAP in biomarker modeling and biological definition of AD.
Biomarkers from blood, as a less invasive and more accessible procedure, can represent the future in establishing a diagnosis through the AD continuum, and guidelines for determining the appropriate therapy. As good screening tools they can be useful in widespread use in daily routine practice.

Disease modifying strategies

Angelo Antonini
University of Padova, Padova, Italy

Parkinson's disease (PD) is the fastest-growing neurological disorder worldwide, presenting significant management challenges due to its progressive disability, the emergence of levodopa-resistant symptoms, and treatment-related complications. Ongoing research priorities for the coming years focus on two key areas: a) slowing disease progression through the integration of sensitive biomarkers and targeted biological therapies, and b) enhancing current symptomatic treatments, including surgical and infusion therapies, to delay complications and improve long-term patient care.
The path to disease modification is complex, hindered by the multifaceted pathophysiology and the diverse mechanisms underlying PD. Current research is addressing alpha-synuclein aggregation, alongside efforts targeting pathways specific to rarer genetic forms of the disease. The success of these initiatives will depend on the development of robust clinical endpoints, the incorporation of advanced technologies, and the identification of reliable biomarkers for early diagnosis and continuous monitoring of disease progression. Several potential biomarkers of degeneration have been explored in the biological fluids, particularly in cerebrospinal fluid (CSF), skin, and blood. These biomarkers include alpha-synuclein, neurofilament light chain, lysosomal markers, inflammatory markers, and microRNA, among others. CSF markers may more accurately reflect changes occurring in the central nervous system compared to other biofluids, which can also be influenced by damage to the peripheral and enteric nervous systems. However, concentration and seeding assays in these tissues still require further validation, especially in large patient cohorts, as outlined below.
In parallel, symptomatic treatment requires a shift in focus towards refining existing approaches and fostering the development of new therapies that address levodopa-unresponsive symptoms and other clinical manifestations that severely impact patients' quality of life.

Axial Postural abnormalities in PD

Michele Tinazzi
University of Verona, Verona, Italy

Postural abnormalities involving the trunk are referred to as axial postural abnormalities and can be observed in over 20% of patients with Parkinson's disease (PD) and in atypical parkinsonism. These symptoms are highly disabling and frequently associated with back pain and a worse quality of life in PD. Despite their frequency, little is known about the pathophysiology of these symptoms and scant data are reported about their clinical predictors, making it difficult to prompt prevention strategies.
We conducted a scoping literature review of clinical predictors and pathophysiology of axial postural abnormalities in patients with parkinsonism to identify key concepts, theories and evidence on this topic. Methods: We applied a systematic approach to identify studies, appraise quality of evidence, summarize main findings, and highlight knowledge gaps.

Ninety-two articles were reviewed: 25% reported on clinical predictors and 75% on pathophysiology. Most studies identified advanced disease stage and greater motor symptoms severity as independent clinical predictors in both PD and multiple system atrophy. Discrepant pathophysiology data suggested different potential central and peripheral pathogenic mechanisms.
The recognition of clinical predictors and pathophysiology of axial postural abnormalities in parkinsonism is far from being elucidated due to literature bias, encompassing different inclusion criteria and measurement tools and heterogeneity of patient samples. Most studies identified advanced disease stage and higher burden of motor symptoms as possible clinical predictors. Pathophysiology data point toward many different (possibly non-mutually exclusive) mechanisms, including dystonia, rigidity, proprioceptive and vestibular impairment, and higher cognitive deficits.

Clinical, MRI, and Laboratory Correlates of Neurodegeneration in Multiple Sclerosis

Gregor Brecl Jakob
University Medical Centre Ljubljana, Ljubljana, Slovenia

Multiple sclerosis (MS) is a chronic autoimmune disease characterized by inflammation, demyelination, and neurodegeneration of the central nervous system (CNS) [1]. While traditionally considered a demyelinating disorder, growing evidence highlights neurodegeneration as a key component of MS, contributing to long-term disability [2-4]. Understanding the clinical, MRI, and laboratory correlates of neurodegeneration in MS is crucial for early detection of disease progression and evaluating treatment efficacy as well as for appropriate treatment decisions.
Clinically, neurodegeneration in MS manifests as both physical and cognitive impairment. Symptoms such as motor dysfunction, sensory deficits, and visual disturbances are common. As the disease progresses, patients often experience a gradual decline in cognitive functions [5], although cognitive impairment can be detected even in the earliest stages of MS [6]. It is difficult to detect these features of disease progression by means of routine neurological examination mandating additional tools and questionnaires to be used in every day clinical practice.
Magnetic resonance imaging (MRI) plays a pivotal role in following inflammatory activity of the disease and treatment decisions in MS. It can also detect features of neurodegeneration. Conventional MRI techniques, such as T1-weighted and T2-weighted imaging, are valuable for identifying brain atrophy and lesion load. Brain atrophy, especially in the cortex and deep grey matter structures like the thalamus, correlates strongly with cognitive decline and disability progression in MS [7, 8]. Newer methods allow detection of cortical lesions which are associated with disability progression [9]. Additionally, advanced techniques can be used to identify slowly expanding and iron rim lesion which are also key MRI correlates of neurodegeneration in MS [10]. However, changes in these parameters are hard to quantify in routine clinical practice without using advanced computerised techniques.
Laboratory correlates of neurodegeneration in MS include biomarkers found in cerebrospinal fluid (CSF) and blood. Neurofilament light chain (NfL), a structural protein released into the CSF and blood following axonal damage, has emerged as a robust biomarker for neurodegeneration in MS. Elevated levels of NfL correlate with disease

activity, brain atrophy, and clinical disability, making it a valuable tool for monitoring disease activity and response to therapy, however they are of limited use to monitor disease progression. Other biomarkers, such as glial fibrillary acidic protein (GFAP) and others, are also being investigated for their potential role in reflecting neurodegenerative processes and CNS damage in MS [11].

To conclude, early detection of disease progression/neurodegeneration remains a challenge in MS. The integration of clinical, MRI, and laboratory data provides a comprehensive understanding of neurodegeneration in MS. Together, these correlates are essential for optimizing patient management, tailoring treatment strategies, and improving outcomes for individuals living with MS and need to be incorporated into everyday clinical practice.

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Epstein–Barr virus and multiple sclerosis: moving from questions of association to questions of mechanism

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Epidemiological studies present evidence that multiple sclerosis (MS) is a rare complication of infection with the Epstein-Barr virus (EBV), a herpesvirus that infects more than 90% of the world's population. A little less than half a century since the connection between the Epstein-Barr virus (EBV) and multiple sclerosis (MS) was discovered, this topic has intrigued the scientific community. Since then, the gradual collection and validation of data has shown that EBV plays a key role in the development of MS. The risk of MS as a neuroinflammatory disease with demyelinating focal lesions of the central nervous system (CNS) is significantly low in EBV seronegative subjects, while the history of infectious mononucleosis (acute symptomatic primary EBV infection) significantly increases the risk of MS. With the data and evidence available today, the mechanisms of this interaction and the EBV-induced immune dysregulation that can cause MS in susceptible individuals must be fully elucidated.
Over the past few years, a number of studies have provided clues about the underlying mechanisms that could help us develop more targeted treatments for MS and a possible discussion of the implications for MS treatment and prevention, including the use of antiviral drugs and vaccines.

Genetic landscape of complex dystonia syndromes

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Complex dystonia syndrome encompasses a diverse range of movement disorders, characterized by the presence of dystonia along with additional neurological or systemic symptoms. Many syndromes or diseases can present with complex dystonia, either as the cardinal sign or as part of a multisystemic manifestation. Complex dystonia often gradually develops in the disease course, but can also be present from the onset. This heterogeneity makes it a challenging condition to diagnose and treat.
The molecular causes of complex dystonias are quite varied, while phenotypic presentations are often beyond the well-known patterns. An ever-expanding spectrum of genes causing diseases that encompass dystonia associated with other neurological and systemic manifestations are discovered with the advances of genetic techniques. Therefore, clinico- radiological algorithms based on the age of onset, additional neurological or systemic features, and imaging findings are emerging for differential diagnosis. Furthermore, the special focus should be on the identification of treatable diseases. Prominent examples are disorders of monoamine neurotransmitter metabolism, Glut1-deficiency syndrome, Niemann–Pick Type C, and Wilson`s disease.
This lecture will be focused on the clinical and radiological clues for the recognition of various genetic complex dystonia syndromes.

Long term efficacy of device aided therapies in advanced parkinson's disease and reasons for switching and combinig them

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Advanced Parkinson's disease with its motor and nonmotor fluctuations causes a significant deterioration of patients' and caregivers' health related quality of life. The cause of fluctuations is complex, however pulsatile dopaminergic stimulation caused by standard oral levodopa intake plays a major role.
Over the last few decades, a concept of continuous dopaminergic stimulation has been introduced to enable more stable non-pulsatile dopaminergic stimulation and neuromodulation. Various device aided therapies (DAT) are nowadays available and routinely used in the treatment of aPD. These are subcutaneous infusion of dopamine agonist apomorphin, subcutaneous infusion of foslevodopa/foscarbidopa, intrajejunal infusion of levodopa/carbidopa gel, intrajejunal infusion of levodopa/carbidopa/entacapone gel and deep brain stimulation of subthalamic or globus pallidus pars interna nuclei. The number of aPD patients treated with DAT is growing, which brings new challenges for patients, caregivers and health care practitioners.
Although the long-term efficacy and safety of the DAT is well established, in some patients there is need for switch among DAT of add an additional DAT. Switching or adding DATs is recommended if the first DAT does not offer a sufficient symptom control or causes side effects. The choice of "new" DAT should be based on the regarding leading symptom or complication of the first DAT. The clinical effectiveness of the initial and modified DAT is comparable.

Atypical' atypical parkinsonism: the catalogue of genetic and immune-mediated mimics

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On the path of dissecting the phenotype of Parkinson's disease (PD) that has lasted for more than 200 years, we have realized that we are no longer talking about one and only PD, but about the spectrum of Parkinson's disease. If we just stay within the PD entity, there are enough diagnostic pitfalls and concerns for us as clinicians.
Furthermore, atypical parkinsonian syndromes (APS), including progressive supranuclear palsy (PSP), corticobasal syndrome (CBS) and multiple system atrophy (MSA), represent another level of diagnostic uncertainty in the spectrum of degenerative parkinsonism, especially in the early stages when they are often misdiagnosed as PD or overlaps with other parkinsonism. But the differential diagnosis and dissection of parkinsonism seems to be a never-ending story, and with the development of genetics and neuro- immunology, we have realized that there is an exhaustive list of conditions that can mimic atypical parkinsonism. They are called 'atypical' atypical parkinsonism or PSP, MSA, CBS- look-alike syndromes or mimics of APS. These conditions are not "major" in the sense of "common", but in the sense of "important to know about because some are hereditary, or even more so - some are treatable". When we are facing patients with clinical hallmarks of APS, we must be aware of diagnostic decision

algorithms which could help us to navigate between degenerative parkinsonism and daunting menu of options for their mimics.
Until now, none of the laboratory institutions could offer all the genetic tests or antibody tests to cover these long lists of parkinsonism mimics, so doctors will have to do some homework, familiarize themselves with the catalogue of these new entities, the approaches to their investigations and their treatment.

The role of stress in neurodegenerative diseases

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Neurodegenerative diseases are a great concern because of aging worldwide population. Despite substantial effort to advance our understanding of the etiology and potential treatment of neurodegeneration, there remains a paucity of information with respect to this complex disease process. Interestingly, stress has been implicated among the potential mechanisms implicated in neurodegenerative pathology.
Stress plays an integral role in disease, including neurodegenerative diseases such as Alzheimer's disease (AD, Parkinson's disease (PD) etc. Exposure to acute or chronic stress affects learning and memory function. Chronic stress accelerates aging, increases inflammation, cortisol, and catecholamines, and induces changes in the gut microbiome.
Individual differences in stress responses depend on how a person perceive a situation and the quality of health when he encounters stress. Stress responses can be modified by many variables: growth factors, bacterial ligands, cytokines, opioids, and adipokines—all modulate glucocorticoid release independent of pituitary ACTH. It was shown that cortisol/stress associations may depend mainly on the types of stressors and stress management mechanisms.
There are difficulties in assessing stress. Older adults have a heightened test environment sensitivity compared to younger adults. When the assessment directions are modified, decreasing emphasis on memory, the elderly perform comparable to the young adults. Perhaps assessing the aging population's cognitive capacities is stressful, stemming from the fear of underlying dementia.
Neurodegenerative disorders such as Alzheimer's, Parkinson's and Huntington's Disease showed an acceleration in disease progression and a worsening of symptoms under stress. Some therapies (e.g., yoga, meditation) focused on reducing stress showed beneficial effects against neurodegeneration. Nevertheless, more studies are necessary in order to completely understand the implications of stress in neurodegeneration and the usefulness of stress reduction in their prevention and treatment.

Functional assessment of endogenous retrovirus mediated neurodegeneration via transcriptome analysis

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The endogenous retrovirus type W (HERV-W) is a human-specific entity, which was initially discovered in multiple sclerosis (MS) patient derived cells1. In the meantime,

a few additional pathologies have been associated with HERV-W induction, such as the recently discovered strong expression levels in Covid19 patients2. In the context of MS, we initially found that the HERV-W envelope (ENV) protein negatively affects oligodendrogenesis3 and controls microglial cell polarization towards a myelinated axon associated- and damaging phenotype4. Such first functional assessments were conducted ex vivo, given the human-specific origin of HERV-W. Recent experimental evidence gathered on a novel transgenic mouse model, mimicking activation and expression of the HERV-W ENV protein in vivo, revealed that all glial cell types are impacted and that cellular fates, differentiation, and functions were changed5. Its overall mode of action thus suggests HERV-W to limit myelin repair, to be involved in microglial axon degeneration and hence to participate in smoldering neuroinflammation. To understandhow this endogenized viral protein modulates cell behavior we determined HERV-W-specific gene signatures in glial cells. To this end, we analyzed transcriptomes of ENV protein stimulated microglialand astroglial cells and compared them to gene signatures of lipopolysaccharide (LPS) stimulated cells, owing to the fact that both ligands can activate toll-like receptor-4 (TLR-4)6. A subsequent comparison between published disease associated glial signatures and HERV-W ENV elicited glial transcriptomes was then conducted using gene set enrichment analysis. This allowed the association of HERV-W triggered microglial cells with particular microglial subclasses observed in MS and Covid19. Such overlapping patterns of regulated genes also facilitate the molecular dissection of pathological processes leading to axonal injury and degeneration. We, therefore, provide here for the first time a detailed molecular description of specific HERV-W ENV evoked effects on those glial cell populations that are involved in smoldering neuroinflammatory processes relevant for progression of neurodegenerative diseases.

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Non invasive brain stimulation in degenerative disorders

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Non-invasive brain stimulation (NIBS) has gained significant attention as a therapeutic tool in the treatment of neurodegenerative diseases. Techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are being explored for their ability to modulate neural activity, enhance neuroplasticity, and potentially alter the course of diseases like Alzheimer's disease, Parkinson's disease, and multiple sclerosis. TMS uses magnetic fields to induce electrical currents in targeted brain regions, promoting changes in cortical excitability that can improve motor and cognitive functions. tDCS, on the other hand, involves applying a low electrical current to the scalp to modulate neuronal activity, which may enhance cognitive processes and alleviate symptoms associated with neurodegeneration.

Research has shown that NIBS can be effective in mitigating some of the motor and cognitive deficits seen in neurodegenerative conditions. For example, in Parkinson's disease, TMS has been reported to improve motor function, reduce tremors, and even alleviate some non-motor symptoms such as depression. In Alzheimer's disease, tDCS has shown promise in enhancing memory and cognitive function, possibly by modulating neural circuits involved in memory processing.

However, the mechanisms underlying the therapeutic effects of NIBS are not yet fully understood. While it is believed that these techniques can promote synaptic plasticity and strengthen neural networks, the long-term effects and potential for disease modification remain subjects of ongoing research. Additionally, the optimization of stimulation parameters, such as intensity, duration, and targeting of specific brain regions, is critical for maximizing therapeutic outcomes.

Despite the need for further studies, particularly large-scale clinical trials, the potential of NIBS as a non-invasive, low-risk intervention makes it an appealing option in the management of neurodegenerative diseases. As research progresses, NIBS may become an integral part of treatment protocols, offering new hope for patients with these challenging conditions.

How do stem cells change expression of genes involved in cell death and autophagy in the neural tissue affected by hypoxia?

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Although many preclinical and clinical trials have reported beneficial effects of stem cells on nervous tissue affected by stroke, molecular mechanisms in the background of documented improvements remain largely elusive.
This research focused on the influence of hypoxic-ischemic injury on the structure and metabolism of mitochondria, on autophagy in immature cells of CNS and on some genes involved in specific forms of cell death (pyroptosis, necroptosis). In experiments for which we used in vitro model of hypoxia/ischemia and a mouse model of stroke, we found that lack of oxygen and glucose has a negative effect on the surface, length and branching of mitochondria. Moreover, hypoxia increased levels of cell death and autophagy. With the aim of finding new therapeutic approaches, cells of CNS damaged by acute lack of oxygen and glucose and animals affected by stroke were treated with neural stem cells or their exosomes. Observed findings which suggested beneficial effects of this approach included reduced level of superoxide anions, cell death and autophagy, alongside reduced levels of expression of genes involved in pyroptosis (GSDMD) and necroptosis (pMLKL).
This research revealed that application of stem cells or their products reduces levels of cell death, which is, to some extent, achieved over reduction of mitochondrial damage and levels of pyroptosis and necroptosis.

Supported by the Croatian Science Foundation Grant DevDown (IP-2022-10-4656) and by the project awarded by the National Recovery and Resilience Programme BrainClock (NPOO.C3.2.R3-I1.04.0089)

Can lamarckism explain cognitive evolution in humans?

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The Darwinian model of evolution, which emphasizes natural selection of random genetic variations, offers an important, but incomplete view in explaining human brain evolution. An older concept by Jean-Baptiste Lamarck suggests that somatic cells pass adaptive information to future generations based on experience. Although this idea was sidelined due to a lack of a known mechanism, recent studies, especially on neurological and psychiatric diseases, indicate that organisms adapt to their environment and pass crucial information to their offspring.
The human brain has tripled in size over the past five million years since diverging from chimpanzees, primarily due to the expanded neocortex. This expansion is believed to underlie enhanced cognitive abilities in humans. While some protein-coding genes have evolved, it is the non-coding regions of the genome that significantly par-

allel human brain development. These non-coding elements, including RNA editing, have increased brain flexibility, leading to advanced cognition and, when dysregulated, neurological and psychiatric diseases.

Dementia and cognitive impairments in the aging population offer insights into evolutionary mechanisms. Next-generation sequencing has shown that de novo mutations, though rare, cluster in specific genetic pathways related to brain function. These mutations also play roles in conditions like schizophrenia and intellectual disability, suggesting that brain evolution is not entirely random but driven by targeted genetic changes with high heritability. The increased risk of cognitive decline and dementia with paternal age points to heritable brain mutations from sperm, supporting the idea of directed de novo mutations, as sperm have a higher mutation rate compared to eggs.

A combination of Darwin's pangenesis and Lamarckian epigenetic modifications, along with new RNA and DNA mutations, appears to drive current cognitive evolution. This requires a mechanism for transmitting adaptive neuronal changes from brain cells across generations. Maternal epigenetic inheritance also occurs under adverse conditions during pregnancy, but sperm provide a broader scope for such mutations.

The human brain's rapid evolution is importantly driven by non-coding RNA mechanisms and Lamarckian inheritance challenging the idea that evolution is solely through random mutations in the germline. Future research may uncover mechanisms of Lamarckian inheritance, mediated by small regulatory RNA-containing vesicles, providing a fuller understanding of brain evolution and its implications for cognitive health and disease.

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Analysis of optineurin variants in neurodegenerative diseases

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The OPTN gene encodes for a multifunctional ubiquitin-binding adaptor protein whose mutations have been linked with amyotrophic lateral sclerosis (ALS), frontotemporal dementia and glaucoma. Here I will discuss differences between optineurin variants reported in these diseases and naturally occurring optineurin variants within an effort to improve pathogenicity prediction and elucidate molecular mechanisms of neurodegenerative process(es).

What is in a name and what is in the brain - a few short dementia stories on genotype/phenotype correlation and protein aggregation

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The ongoing year holds exiting insights in understanding neurodegenerative diseases, but also to a degree disappointment in the light of the "great expectations" regarding treatment. The lecture is a viewpoint drawing analogy from Shakespeare's famous query, "What's in a name?" and explores what defines neurodegenerative diseases such as Parkinson's (PD) and Alzheimer's (AD) and what clinicians understand by that name in relation to the underlying brain pathology and disease biology. The inspiration comes from the latest biological definitions of Parkinson's disease revealing significant similarities with the biological definition of Alzheimer's disease (AD), recently reshaped by the newly revised diagnostic criteria. Structured as a play, the lecture explores the similarities, differences, flaws and advantages of these biological definitions of PD and AD. The prologue brings the recent advances in the field in the spotlight, followed by the first act: Walking straight into circles, reflecting on the slight imperfections of these concepts, keeping us walking in circles while thinking we are moving forward in the right direction, towards clinically meaningful treatment. With the latest news on EMA's decision not to approve lecanemab for AD treatment, critical thoughts have arisen regarding the disease neurobiology and treatment approach. Even though biological definitions of NDDs are paving the way for future breakthroughs in neurodegenerative disease management, slight misinterpretations as equating pathology and biology of a disease could be misleading in defining treatment targets. Understanding NDDs

through the lens of proteinopathies requires critical thinking as the presence of protein aggregates to a certain degree is a consequence rather than a root cause, a debris of preceding complex mechanisms interplay disrupting proteostasis, of damage response failures, or even a long-preserved protective brain response. Recent developments have sparked a new, thought-provoking perspective, explaining Alzheimer's disease (AD) and Parkinson's disease (PD) not as proteinopathies but rather as proteinopenias, suggesting potential treatment approaches from a different angle.

The second act, "What's in a Name and What's in the Brain", presents few dementia stories, each one posing a question in search of an answer regarding genotype/phenotype and underling pathology/biology correlation. A novel APP mutation in EOAD with marked parkinsonism and visual hallucinations; SQSTM1 mutation in bv FTD associated with amyloid β proteinopathy; and phenotypic variability in C9orf72 expansion mutation. The emerging questions aim to understand the correlation between observed phenotype, genotype and (un) expected underlying protein aggregation, to understand the occurrence and significance of co-pathologies, and to explore drivers of phenotypic variability. In the era of biologically defining neurodegenerative diseases, answers to these questions (sought for a long time, some partly answered), are crucial prior clinically widespread use of biomarkers and biological classification of NDDs and must be considered in treatment decisions and disease management (not necessarily focused on clearing protein aggregates only, but rather on addressing upstream disturbances earlier in the disease neurobiology including prevention).

The epilogue brings contemplation owing to the recently published papers European intersocietal recommendations for the biomarker-based diagnosis of neurocognitive disordersand Refining the clinical diagnosis of Parkinson's disease that successfully integrate clinical reasoning with the biological understanding of AD and PD. We are undoubtedly moving in a direction where clinicians have the mindset of both a researcher and a pathologist. However, on this challenging path, we must ensure that clinicians are not "lost in translation" while coding and decoding NDDs, striving to align clinical diagnoses with the underlying brain pathology and biology to ensure more effective treatment outcomes in the future.

Parkinson's disease risk and mechanisms from military relevant organophosphate exposures

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Military service has long been known to increase the risk for the development of neurodegenerative diseases, including Parkinson's disease. While the military-specific risk factors remain incompletely identified, environmental exposures, stress/exertion, and traumatic brain injury. With respect to environmental exposures, chemical warfare agents have been extensively studied. However, high-use pesticide exposures are a likely frequent and chronic exposure that is now just gaining prominence. Organophosphate exposures, specifically the pesticide chlorpyrifos, have been anecdotally reported to be

quite high in military settings. While chlorpyrifos has been primarily studied as an acetylcholinesterase inhibitor, emergent epidemiological studies and basic science experiments have linked exposure to Parkinson's disease risk. Our studies have aimed to test the hypothesis that military-relevant chlorpyrifos produces dopaminergic neurotoxicity relevant to Parkinson's disease pathology and association with Parkinson's disease risk in humans. Our laboratory studies have utilized neuronal cell culture and animal models. To date, we have shown that while chlorpyrifos is indeed able to produce cholinergic deficits, these deficits occur at higher doses that are required to produce dopaminergic neurotoxicity. Moreover, upon removal of exposure, cholinergic deficits are ameliorated, while dopaminergic deficits persist. Repeated dosing in rodents has produced a motor phenotype relevant to Parkinson's disease, at doses below that which produce cholinergic dysfunction, further supporting findings from in vitro studies. Additionally, semi-quantitative immunofluorescence analysis identified a decrease in dopaminergic striatal density in chlorpyrifos treated rodents versus controls. This reduction in striatal terminal density supports the notion that the observed neurobehavioral deficits arising from chlorpyrifos are due to dopaminergic neurotoxicity. Ongoing studies are testing for possible associations between increased likelihood of chlorpyrifos exposure among Parkinson's disease cases, as well as progression. Taken together, our translational studies, along with the scientific literature suggest mechanistic and possible risk links between military-relevant chlorpyrifos exposure and Parkinson's disease.

How can non-pharmacological interventions support a person with cognitive impairment?

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Non-pharmacological interventions play a crucial role in supporting individuals with cognitive impairment, offering alternative approaches to managing symptoms and enhancing quality of life. These interventions focus on psychological, social, and environmental strategies that can be tailored to individual needs, providing a holistic approach to care.

One of the primary non-pharmacological interventions is cognitive stimulation therapy (CST), which involves structured activities and exercises designed to improve cognitive function. CST can include memory games, puzzles, and problem-solving tasks that help maintain mental agility. Studies have shown that CST can lead to improvements in memory, language skills, and overall cognitive function, often resulting in enhanced mood and quality of life.

Behavioral interventions are also essential, targeting the management of challenging behaviors such as agitation, aggression, and depression. Techniques such as behavior modification, positive reinforcement, and the implementation of structured routines can reduce the frequency and severity of these behaviors. For instance, identifying triggers for agitation and developing strategies to avoid or minimize these triggers can lead to significant behavioral improvements.

Environmental modifications are another effective strategy. Creating a safe, supportive, and stimulating environment can significantly impact an individual's well-being. This can include adjustments like improved lighting, reducing clutter to minimize confu-

sion, and incorporating familiar objects and photos to provide comfort and aid memory. Additionally, ensuring regular physical activity and social engagement is vital. Exercise has been shown to improve physical health, mood, and cognitive function, while social activities can reduce feelings of isolation and depression.
Therapeutic approaches such as music therapy, art therapy, and reminiscence therapy offer additional benefits. Music therapy can enhance mood, reduce anxiety, and promote social interaction, while art therapy provides an outlet for expression and creativity. Reminiscence therapy, which involves discussing past experiences and memories, can improve mood, cognitive function, and provide a sense of identity and continuity.
Support for caregivers is also a crucial component of non-pharmacological interventions. Educating caregivers about effective communication strategies, behavior management techniques, and stress reduction methods can enhance the care they provide and improve their own well-being. Support groups and respite care are vital resources, offering emotional support and practical assistance, helping to prevent caregiver burnout.
In conclusion, non-pharmacological interventions offer a comprehensive and individualized approach to managing cognitive impairment. Through cognitive stimulation, behavioral interventions, environmental modifications, therapeutic activities, and caregiver support, these strategies can significantly enhance the quality of life for individuals with cognitive impairment and their caregivers. The holistic nature of these interventions ensures that they address the diverse and complex needs of this population, providing meaningful and sustainable improvements in their daily lives.

Free-water imaging in Parkinson's disease

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Diffusion tensor imaging (DTI) is an MRI imaging technique that is sensitive to molecular diffusion. DTI can produce several useful values for each voxel in the volume, namely fractional anisotropy (FA), mean diffusivity (MD) and apparent diffusion coefficient (ADC). FA, MD and ADC values and other DTI metrics are tissue-specific only if the voxel contains a single tissue type, which is not true in many cases due to the partial volume effects (PVE) inside the voxel. A common source of PVEs in MRI of brain tissue are free water molecules (FW). Effects of extracellular FW on DTI-derived metrics can be corrected with a bi-tensor compartment model. Results of the model are standard DTI-derived metrics without FW influence, as well as FW partial volume maps. Research has shown that partial volume of FW in substantia nigra (SN) longitudinally increases in Parkinson disease. Goal of this work was to implement a method of FW partial volume determination in brain DTI MR data. Second goal was to assess whether this method can produce consistent results using 1.5 T MRI data. DTI protocol used to acquire imaging data consists of two DWI sequences and one 3D high resolution T1-weighted sequence. One DWI sequence uses 30, and the other 60 noncolinear diffusion directions in spherical distribution. FMRIB software library (FSL) tool was used for brain extraction, eddy current correction and spatial registration of all volumes to b0 volume. Diffusion imaging in Python (DIPY) library was used to calculate standard DTI-derived metrics, maps and parameters. A standalone program in Python was written to calculate FW maps and FW-

corrected DTI-derived metrics using a preexisting algorithm. Preliminary results show that FW maps in SN region of the brain have average value of 0.161 ± 0.036 for control group, and 0.195 ± 0.034 for patients with diagnosed Parkinson disease, which is in line with results from previous scientific articles.

Keywords: diffusion tensor imaging, fractional anisotropy, free water molecules, Parkinson disease

Microbiota in neurodegenerative disorders

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Gut microbiota is a complex system, producing all sorts of protective compounds and acting as a barrier against pathogens. Neurons, as we know, gradually deteriorate in neurodegenerative illnesses, causing impairment in cognitive and physical function, significant disability and a decline in the quality of life of patients. The role of the "gut-brain axis" and microbiota started drawing more attention in investigating the pathogenic mechanism of many neurodegenerative diseases like Parkinson's disease (PD), Alzheimer's disease (AD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), etc.
Studies have shown altered gut microbiota composition in people with these illnesses, and it is one of the most critical lines of evidence connecting gut microbiota dysbiosis to neurodegenerative diseases. AD patients have a distinct characteristic of having a particular microbiota profile. Similar changes in the gut microbiota composition have been noted in people with MS, ALS and PD. Nevertheless, dysbiosis may influence the onset and progression of neurodegenerative diseases. In order to emphasize any potential underlying mechanisms and examine potential treatment repercussions, the lecture's goal is to summarize current knowledge about the connection between gut microbiota and neurodegenerative disorders mostly PD, AD, ALS and MS.

Keywords: gut microbiota, amytrophic lateral sclerosis, multiple sclerosis, neurodegenerative diseases, Alzheimer's disease, Parkinson' s disease