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

5th RIJEKA FORUM ON NEURODEGENERATIVE DISEASES
NEURODEGENERATIVE DISEASES: TOWARD THERAPY

ACADEMIA SCIENTIARUM ET ARTIUM CROATICA
MDCCCLXI

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Rijeka, November 08-09, 2021

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Registration: online via registration form for online participants

Event address for ZOOM attendees will be sent to all registered participants by e-mail

Free admission for registrations

Information

Željana Mikovčić, Department of Biomedical Sciences in Rijeka
Radmile Matejčić 2, Rijeka
Phone: 051 584 826, e-mail: rimed@hazu.hr
Vivid original d. o. o., Zagreb
Phone: +385 (0)98 508 502; e-mail: info@vivid-original.com
Anja Turkalj Mahmutović, LLM, Department of Neurology,
Cambierieva 17/8, Rijeka
Phone +385 (0)51 658 311 e-mail: neurologija@kbc-rijeka.hr

OPENING
(9:00-9:30)

Introduction

Daniel Rukavina, M.D., PhD, Professor Emeritus, Head of the Department of Biomedical Sciences in Rijeka, Croatian Academy of Sciences and Arts

Vladimira Vuletić, M.D., PhD, Assistant Professor, Medical Faculty, 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, Head of the Clinical Hospital Center, Rijeka, Croatia

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

Snježana Prijić Samaržija, PhD, Professor, Rector, The University of Rijeka, Rijeka, Croatia; President, Young European Research Universities Network (YERUN)

P R O G R A M
1st day – November 08th, 2021

9,30 – 11,00 h

I. GENETIC ASPECTS

Chairmen: Borut Peterlin and Nenad Bogdanović

John Hardy, M.D., PhD, Professor, UCL Institute of Neurology, London, UK
Genetic analysis of decline of disease rate

Nir Giladi, M.D., Professor,Neurological Institute, Tel Aviv Medical Center – Ichilov; Sackler School of Medicine, Sagol School of Neuroscience, Tel Aviv University, Israel
Genetic Parkinson's disease, the story of GBA and LRRK2 PD among the Ashkenazi Jews

Borut Peterlin, M.D., PhD, Professor, University Clinical Center Ljubljana, Ljubljana, Slovenia
Advanced therapies for genetic neurodegenerative disorders

Break for refreshment: 10:50 – 11:00

11,00 – 12,30 h

II. NEUROMODULATION AND NEURODEGENERATION

Chairmen: Zvezdan Pirtosek and Vladimira Vuletic

Elena Moro, PhD, Movement Disorders Unit, Department of Psychiatry, Neurology, Neurological Rehabilitation and Forensic Medicine,Centre Hospitalier Universitaire de Grenoble, Grenoble Alpes University, Grenoble, France
Neuromodulation and neurodegeneration: Hypes, hopes, and actualities?

Zvezdan Pirtošek, M.D., PhD, Professor, University Hospital Centre Ljubljana, Ljubljana, Slovenia
Cellular senescence in brain aging and neurodegenerative diseases: the role of senolytics?

Federica Provini, M.D., PhD, IRCCS Institute of Neurological Sciences, UOC NeuroMet, Bellaria Hospital and Department of Biomedical and NeuroMotor Sciences, University of Bologna, Bologna, Italy
Sleep disorders in synucleionopathies

Lunch break: 12:30 – 13:00

13,00 – 15,20 h

III. ALZHEIMER DISEASE AND DEMENTIAS

Chairmen: Nenad Bogdanović and Alessandro Padovani

Nenad Bogdanović, M.D., PhD, Professor, Department for Neurobiology, Caring Science and Society, Division of Clinical Geriatrics, Karolinska Institute, Stockholm, Sweden
Dementia with Lewy Bodies

Kaj Blennow, M.D., PhD, Professor, Gothenburg University, Gothenburg and Mölndal Campus, Mölndal, Sweden
Recent developments on amyloid/tau and neurodegeneration

Alessandro Padovani, M.D., PhD, Professor, University of Brescia, Institute of Neurology, Brescia, Italy
The usefulness of biomarkers for Alzheimer Disease profiling

Vida Demarin, M.D., PhD, Professor, President of International Institute for Brain Health, Head of Department of Medical Sciences of the Croatian Academy of Sciences and Arts, Zagreb, Croatia
Healthy lifestyle in prevention of neurodegenerative diseases

Break for refreshment: 15:20 – 15:40

15,40 – 16,40 h

Fran Borovečki, M.D., PhD, Professor, University Hospital Centre Zagreb, Zagreb, Croatia
News in treatment of Alzheimer's disease

Gabriela Novotni, M.D., PhD, University Clinic of Neurology, Medical Faculty, University "Ss Cyril and Methodius", Skopje, Macedonia
Alzheimer's disease and resilient brains

Nataša Klepac, M.D., PhD, Assistant Professor, University Hospital Centre Zagreb, Zagreb, Croatia
Cognitive rehabilitation

2nd day – November 9th, 2021

9,00 – 11,00 h

IV. PARKINSON DISEASE

Chairmen: Maja Trošt and Fran Borovečki

Maja Trošt, M.D., PhD, Assistant Professor, University Hospital Centre Ljubljana, Ljubljana, Slovenia
Role of pumps in Parkinson's disease

Vladimira Vuletić, M.D., PhD, Assistant Professor, Clinical Hospital Center Rijeka, Rijeka, Croatia
Microbiota and Parkinson's disease

Slavica Kovačić, M.D., PhD, Department of Radiology Clinical Hospital Center Rijeka, Rijeka, Croatia
Brain MRI in the diagnostic follow-up of Parkinsonism

Darko Chudy, M.D., PhD, Professor, Department of Neurosurgery, University Hospital Dubrava, Zagreb, Croatia
DBS therapy for the vegetative state and minimally conscious state

Break for refreshment: 11:00– 11:15

11,15 – 12,40 h

V. MULTIPLE SCLEROSIS AND OTHER TOPICS

Chairmen: Martin Rakuša and Mario Habek

Gregor Brecl Jakob, M.D, PhD,, Department of Neurology, University Medical Centre Ljubljana, Ljubljana, Slovenia
Can we slow down neurodegeneration in MS?

Mario Habek,M.D., PhD, Professor, University Hospital Centre Zagreb, Zagreb, Croatia
Importance of early treatment of multiple sclerosis with high efficacy disease modifying therapies

Zdravka Poljaković, M.D., PhD, Professor, Medical Faculty, University of Zagreb, Zagreb
Is stroke a neurodegenerative disease?

Lunch break: 12:40 – 13:10

13,10 – 15,40 h

Tamas Revesz M.D.**,** PhD, FRCPath, Professor Emeritus in Neuropathology, University College London UCL Queen Square Institute of Neurology, London, UK
What can we learn from the neuropathological study of corticobasal degeneration (CBD)

Tomislav Babić, M.D., PhD, Professor, Neuroscience Franchise Worldwide Clinical Trials, London **Drug development in Frontotemporal dementia**

Ivana Munitić, M.D.**,** PhD, Professor, Department of Biotechnology, University of Rijeka, Croatia
Neuroimmunity in Amyotrophic lateral sclerosis (ALS)

Paolo Manganotti, M.D., PhD, Professor, Direttore Clinica Neurologica, Azienda Ospedaliero-Universitaria, Ospedale di Cattinara Trieste, Italy
Clinical Neurophysiology and neurodegenerative diseases

Martin Rakuša, M.D., PhD, Assistant Professor, Department of Neurology, University Medical Centre
Maribor, Slovenia
Clinical neurophysiology - diagnostic procedures in patients with Alzheimer's disease

15,40 – 16,10 h

VI. GENERAL DISSCUSION

Moderators: Vladimira Vuletić and Nenad Bogdanović

ABSTRACTS

Genetic analysis of decline of disease rate

John Hardy
UCL Institute of Neurology, London, UK

Early onset Alzheimer's disease can be caused by gene duplications of the APP locus and other causes of early onset disease either increase the production of Aβ or decrease the solubility of the Aβ by changing marginally the position of the APP cleavage. Autosomal dominant tangle disease can be caused by duplication of the MAPT locus or by splice site mutations which increase the proportion of 4 repeat tau transcripts. Finally autosomal dominant Lewy body disease can be caused by synuclein gene duplications. In all these cases, these causes of disease are very rare. They are, however, informative, since they clearly show that these proteins, Aβ, tau and synuclein are close to their deposition thresholds.
As we started to analyses the much more common and generally sporadic late onset forms of these diseases, in general we did not find variants which increased the production of these proteins, but rather, found genes encoding protein s in pathways related to protein and damage clearance. This were generally microglial in Alzheimer's disease, ubiquitin proteasomal in tangle diseases and lysosomal in Lewy body diseases. These finding are consistent with the general thesis that late onset diseases are predisposed to by failures in protein clearance with the different clearance pathways being responsible for different types of clearance: microglial for Aβ, ubiquitin proteasome for tau and lysosomal for synuclein.

Genetic Parkinson's disease, the story of GBA and LRRK2 PD among the Ashkenazi Jews

Nir Giladi
Neurological Institute, Tel-Aviv Medical Center, Tel-Aviv University

Twenty-five years ago we first observed the association between mutations in the GBA gene and Parkinson's disease (PD). Five years later a seminal NEJM paper have confirmed the strong association among the Ashkenazi Jews (AJ) and in 2010 another NEJM paper have established the significant role of mutations in the GBA gene and PD worldwide. Over the past decade GBA-PD has become the most important and most frequent genetic PD.
In parallel, in 2004 the first report about the role of the G2019S mutation in the LRRK2 gene among AJ patients was published in the NEJM. Over the past 15 years those 2 genes, GBA and LRRK2 have been established as the main players in genetic PD globally with about 1\3 of the AJ PD patients carrying mutations in one or both genes. Interestingly, the clinical course associated with GBA or LRRK2 PD are very different, GBA-PD being a relatively malignant disease with early cognitive disturbances and faster rate of progression while LRRK2 PD being relatively benign with relatively preserved cognition and better longevity.

The relatively homogenic genetic background of the Ashkenazim makes them an ideal population to study prodromal phase, genetic modifiers, the role of dual mutations and penetrance.

Sleep disorders in synucleinopathies

Federica Provini [1,2]
[1]IRCCS Istituto delle Scienze Neurologiche di Bologna, Italia
[2]Department of Biomedical and NeuroMotor Sciences, University of Bologna, Bologna, Italy

There is increasing interest in the effects of sleep and sleep disturbances on the brain, including the potential role of sleep disorders in the progression of neurodegeneration. Sleep and circadian rhythm disturbances are central features of many neurodegenerative disorders, exacerbating symptoms and substantially impairing quality of life. Sleep disturbances are among the most frequent non-motor manifestations in Parkinson disease (PD), the second most common neurodegenerative disorder. In PD sleep disturbances comprise the entire spectrum of sleep disorders, including excessive daytime sleepiness, insomnia, restless legs syndrome, rapid eye movement sleep behavior disorder (RBD), and sleep sleep-disordered breathing (SDB). Patients diagnosed with PD and primary sleep disorders tend towards more severe clinical features, including increased motor symptom severity, autonomic dysfunction and cognitive impairment. The literature on sleep disturbances in Parkinsonism such as multiple system atrophy (MSA) and dementia with Lewy bodies (DLB) is not as robust as that in PD. To date, the literature has focused mainly on RBD as the most prominent sleep disorder in MSA and DLB, because RBD has emerged as the most reliable prodromal biomarker for the alpha synucleinopathies, often preceding motor symptom onset by several years. Several sleep-related breathing disorders, including stridor and central and obstructive sleep apneas, frequently occur in MSA. Stridor has been included in the diagnostic criteria as additional feature for the diagnosis of possible MSA, showing a high diagnostic positive predictive value. Little is known about the prevalence and the impact of sleep-disordered breathing in DLB.
These aspects and specific considerations about diagnosis and treatment of sleep disorders in patients with synucleinopathies will be reviewed.

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Dementia with Lewy Bodies

Nenad Bogdanovic[1,2]
[1]Karolinska University Hospital, Stockholm, Sweden
[2]Karolinska Institute, Stockholm, Sweden

Lewy bodies are intraneuronal cytoplasmic inclusions comprising aggregates of α-synuclein and are readily detected by immunohistochemistry using anti–α-synuclein antibodies. Neuropathological studies indicate that Lewy body accumulation follows a stereotypic pattern starting in the brainstem nuclei/olfactory regions and progressing to limbic areas and, in the most advanced stages, to the neocortex. Lewy bodies may also be found concentrated in the amygdala without significant involvement of the brainstem or neocortical regions what is a rare but clinically important variation. Those neuropathological features are related to the specific clinical picture in Dementia of Lewy Body (DLB). It targets a different set of cognitive functions – specifically problem-solving and reasoning, hallucinations that occur early, REM sleep disorder, disruption of the autonomic nervous system and Parkinson's-like movement signs. In DLB memory can vary significantly such that on one day your grandmother might not recognize you and the next day, she can recall the names of each of her grandchildren. One of the early symptoms of DLB is difficulty walking, a decrease in balance and ability to control physical movements. These symptoms are similar to Parkinson's disease. Frequent falling is also common early in DLB. Some people who have DLB display a flat affect, where their faces show very little emotion. This is another symptom that may present early in the disease and overlaps with Parkinson's. Visual hallucinations are typical in DLB , where people see things that aren't actually there, and typically occur earlier in the progression of DLB. Patients with DLB experience REM sleep behavior disorder, a dysfunction where they physically act out the situations in their dreams. Some research suggests that REM sleep behavior disorder can be one of the earlier predictors of DLB. Patients with DLB have a very high risk of serious side effects if antipsychotic medications are given to them. Up to 50% of patients with DLB who are treated with any antipsychotic medication may experience severe neuroleptic sensitivity, such as worsening cognition, heavy sedation, increased or possibly irreversible parkinsonism, or symptoms resembling neuroleptic malignant syndrome (NMS), which can be fatal. The median survival time for patient with DLB is 7.3 years. Men have a higher chance of developing DLB than women do. DLB is a multi-system disease and typically requires a comprehensive treatment. It is important to remember that some people with DLB are extremely sensitive or may react negatively to certain medications used to treat Alzheimer's or Parkinson's in addition to certain over-the-counter medications. Cholinesterase inhibitors are considered the standard treatment for cognitive symptoms in DLB. The patients with DLB may be even more responsive to these types of medications than those with Alzheimer's. The combination of AChEI and memantine is considered as a ground treatment of DLB. Of non-pharmacological treatment several domains are important. Physical therapy options

include cardiovascular, strengthening, and flexibility exercises, as well as gait training. Speech therapy especially method LSVT (Lee Silverman Voice Treatment) may be helpful for low voice volume and poor enunciation. Speech therapy may also improve muscular strength and swallowing difficulties. Occupational therapy may help maintain skills and promote function and independence. Individual and family psychotherapy can be useful for learning strategies to manage emotional and behavioral symptoms and to help make plans that address individual and family concerns about the future. Support groups may be helpful for caregivers and persons with DLB to identify practical solutions to day-to-day frustrations, and to obtain emotional support from others. Since these patients use to end up on the different departments, psychiatry, neurology, internal medicine, orthopedic surgery or geriatric, the most important act is to increase awareness and knowledge of DLB which is the second most frequent dementia

Recent developments on amyloid/tau/neurodegeneration/glial (ATNG) blood tests for Alzheimer's

Kaj Blennow[1,2]
[1]Insitute of Neuroscience and Physiology, University of Gothenburg, Gothenburg, Sweden
[2]Sahlgrenska University Hospital, Mölndal, Gothenburg, Sweden

The new disease-modifying immunotherapies for Alzheimer's disease (AD) calls for simple and widely available screening tests, as well as exact and reliable diagnostic tests for brain amyloidosis (A), but also tau pathology (T) and neurodegeneration (N).
The cerebrospinal fluid (CSF) biomarkers Aβ42 (reflecting brain amyloidosis), phospho-tau P-tau181 (reflecting tau pathology) and total the neurodegeneration biomarkers tau (T-tau) and neurofilament light (NFL), has been extensively validated clinically and show very high diagnostic performance. Both the CSF Aβ42/40 and P-tau/Aβ42 ratio show excellent concordance with amyloid PET, suggesting that the CSF test and amyloid PET are interchangeable for the detection of brain amyloidosis.
Technical developments have given analytical tools to measure some of these protein biomarkers also in blood samples. The plasma Aβ42/40 ratio shows high concordance with amyloid PET in individual cohorts, but the fold change (percent reduction) of the Aβ42/40 ratio is much smaller in plasma (10-15%) as compared with CSF (45%), meaning plasma tests for Aβ42/40 ratio will have robustness issues for clinical routine use.
Different ultrasensitive Immunoassays has been developed to measure several P-tau variants (P-tau181, P-tau217 and P-tau231) in plasma samples. Results from several clinical cohorts show that plasma P-tau is markedly increased in AD, and can distinguish AD from other tauopathies and neurodegenerative disorders (e.g. FTD, PSP/CBD, PD) with very high AUC values. Importantly, plasma p-tau181 increases with more severe tau pathology assessed by tau PET but is also increased in the very early phase of AD, in amyloid PET positive but tau PET negative (Braak stage 0) individuals.
While plasma T-tau works well to identify acute neuronal injury, for example in patients with hypoxic or traumatic brain injury, it doesn't work as a neurodegeneration biomarker for AD in plasma. Instead, neurofilament light (NFL) is a sensitive blood biomarker for neurodegeneration but is not AD-specific.

Alzheimer's disease and resilient brains

Gabriela Novotni[1], Antoni Novotni[2]
[1]University Clinic of Neurology, Medical Faculty-University Ss Cyril and Methodius-Skopje, Skopje, North Macedonia
[2]University Clinic of Psychiatry, Medical Faculty-University Ss Cyril and Methodius-Skopje, Skopje, North Macedonia

When it comes to explaining the complex pathogenesis of Alzheimer's disease (AD), the most common cause for dementia threatening to become an epidemic of the 21st century, the amyloid cascade hypothesis has had the leading role for the last 30 years. In the light of this hypothesis, amyloid has been given the central role as the Holy Grail in AD treatment research for years. Yet, witnessing repetitive clinical trials failures, one inevitably asks if amyloid has been the wrong target? After 18 years since the last AD therapeutic approval, FDA recently approved the first disease modifying treatment (DMT) for AD, aducanumab, a monoclonal antibody targeting amyloid beta, shadowed by controversies regarding its efficacy.

The ongoing AD drug research quest elicits questions that go beyond amyloid and open new horizons in AD treatment. Looking for an answer to a very simple question on why some individuals can tolerate abundant AD pathology in the brain, without clinical manifestation of dementia, may hold the key to future therapeutic strategies. Studies on resilient brains provide valuable information on protective mechanisms, the role of microglia and astrocytes, patterns of synaptic loss and suppressed neuroinflammatory response as the key gatekeeper of AD resilience.

This lecture aims to review and discuss recent findings and new insights into AD pathogenesis, emphasizing the importance of neuroinflammation explained by the Innate Immune Protection Hypothesis. According to this hypothesis, amyloid beta has an important antimicrobial and neuroprotective role, and it is the neuroinflammation that leads to extensive neuronal death and dementia.

Having neuroinflammation as a possible target for AD treatment and prevention, gives hope for developing future therapeutics and adopting lifestyle that combats chronic inflammation.

Cognitive rehabilitation

Nataša Klepac[1,2]
[1]Clinical University Hospital Zagreb, Zagreb, Croatia
[2]Faculty of Medicine, University of Zagreb, Zagreb, Croatia

Normal aging is accompanied by alterations in brain structure and function and associated cognitive changes. Although declines in cognition attributed to the normal aging process are well documented, some of these changes may be related to neurodegenerative diseases such as Alzheimer's disease (AD) and other types of dementia. In an aging population with increasing incidence of dementia and cognitive impairment, strategies are needed to slow age-related decline and reduce disease-related cognitive impairment in older adults. Epidemiological studies report reduced risk for dementia in older adults who maintain higher levels of cognitive activity. Cognitive rehabilitation is the collective label for a wide range of therapeutic interventions. It refers to a set of interventions that aim to improve a person's ability to perform cognitive tasks by retraining previously

learned skills and teaching compensatory strategies. These share a common purpose, to reduce the adverse effects that cognitive impairments have on a person's ability to perform everyday activities, their social role participation and quality of life. There are two very different approaches known as restitutive and compensatory. Techniques using the restitutive approach aim to alter the underlying cognitive impairment. Compensatory techniques include teaching strategies to make behavioural adjustments. The emphasis in compensatory strategies is on coping with and finding ways of adapting to existing impairments. Restitution approaches are more often used in the early stage of the stroke pathway when plasticity is thought to be greatest, and compensatory strategies are typically used later. The core premise of cognitive rehabilitation therapies is based on neuronal plasticity. The nervous system has the ability to adjust its structural organization in response to the environment. The brain has the capability for restructuring itself to adapt to changing circumstances or novel stressors and this happens in normal older adults with plasticity-promoting train. Training can drive brain plasticity by engaging adults in stimulating cognitive activities on a concentrated basis. The training re-engages and fortifies the neuromodulatory systems that control learning, with the goal of increasing the power of cortical representations. Studies indicate that cognitive enhancement therapies (cognitive rehabilitation) can alter brain function at the molecular and synaptic levels, as well as at the neural network level. At the cellular level, this net change in neuronal activity may reflect greater activation of a minority of neurons as a result of the intervention stimulus. To date, cognitive training has been successfully used to target cognitive impairments in other disorders such as stroke, head injury, and substance abuse. The unique circumstances surrounding Alzheimer's disease and other dementia present distinctive challenges for the effective administration of cognitive rehabilitation. Although some clinical trials of cognitive rehabilitation interventions demonstrate positive effects on cognitive performance in this population of patients, other trials show minimal to no effect. Although further research is needed, cognitive rehabilitation interventions aimed at improving brain health through neuroprotective mechanisms show promise for preserving cognitive performance. Cognitive rehabilitation programs that are structured, individualized, longer duration, and multicomponent show promise for preserving cognitive performance in older adults.

The role of pumps in Parkinson's disease

Maja Trošt[1,2]
[1]University Medical Centre Ljubljana, Ljubljana, Slovenia
[2] Medical Faculty, University of Ljubljana, Ljubljana, Slovenia

Treatment of Parkinson's disease (PD) is symptomatic. Levodopa is still the gold standard and the most effective medication for PD and most PD patients are treated with levodopa in the course of their disease. At the same time, neither levodopa nor any other available medical treatment modulates the progressive course of neurodegeneration in PD patients. Numerous animal studies have shown that the pulsatile levodopa intake cause cellular aberrations in PD. Single levodopa dosages cause pathologically high levels of dopamine in striatum followed by pathological drop. These unphysiological fluctuations in striatal dopamine levels (primarily due to short levodopa half- life) together with the progression of neurodegeneration are believed to be the main reason for levodopa induced motor complications in advancing PD.

Continuous dopaminergic drug delivery mimics a more physiologic conditions in striatum and delays the onset and reduces the severity of motor complications. There are various possibilities to achieve continuous dopaminergic stimulation (CDS): administering more smaller doses of levodopa or dopamine agonists which have longer half-life then levodopa and can be administered once daily orally or trans-dermally. About twenty percent of PD patients reach the disease the stage with sever motor fluctuations and/or dyskinesia, in which oral or trans-dermal application of dopaminergic medication do not sufficiently improve patients' quality of life. In those, parenteral infusion of dopaminergic medication aided with pumps, is necessary.
Nowadays, apomorphine continuous subcutaneous infusion, levodopa/carbidopa intestinal gel infusion and levodopa/carbidopa/entacapone intestinal gel infusion are available. They all significantly reduce the severity of levodopa induced motor complications and improve PD patients' health related quality of life. New treatment formulations, like subcutaneous levodopa infusion are under development.

Microbiota and Parkinson's disease

Vladimira Vuletić[1,2]
[1]Clinical Hospital Center Rijeka, Rijeka, Croatia
[2] Medical faculty University of Rijeka, Rijeka, Croatia

Parkinson's disease (PD) is the second most common chronic age-related, progressive neurodegenerative disorders. The hallmark symptoms of PD include motor features (bradykinesia, postural disturbances, rigidity or tremor or both) and nonmotor features (hyposmia, gastrointestinal (GI) symptoms, sleep disorders, autonomic, neuropsychiatric and sensory symptoms). In PD, despite remarkable advances in our insight into the responsible mechanisms, the etiology remains unknown. The key neuropathology in PD is Lewy body (LB) deposition (abnormal aggregates of a misfolded protein called α-synuclein) and consequently neuronal dysfunction, involving many other brain areas and neurotransmitter systems. In their early research, Brack et al. proposed a staging scheme based on rostro-caudal pathological progression and it was suggested that in the earliest stages, PD damage is confined to non-dopaminergic structures in the lower brainstem, the olfactory bulb or perhaps the peripheral autonomic nervous system, accounting for the early appearance of non-motor symptoms.
Also, patients with Parkinson's disease (PD) were often observed with gastrointestinal symptoms (up to 80% have constipation), which preceded the onset of motor symptoms. Neuropathology of PD has also been found in the enteric nervous system (ENS). Many studies have reported significant PD-related alterations of gut microbiota. In the other report, Braak staging traced the course of pathology, stating that PD started when a pathogen enters the body *via* the nose or the GI system, leading to the formation of LBs and spreading from the enteric nervous system (ENS) to the central nervous system (CNS) through the vagus nerve. Therefore, the role of the "gut-brain axis" started drawing more attention in investigating the pathogenic mechanism of PD. PD-derived gut microbiota could enhance α-synuclein-mediated motor deficits and brain pathology in an animal models. Thus, intestinal microbiota disturbance could be considered as a potential risk factor for PD. Gut microbiota is a complex system, producing all sorts of protective compounds and acting as a barrier against pathogens. Growing evidence has indicated that the abnormality of gut microbiota and its metabolic products may be triggers for the formation of LBs in the ENS.

There are a lot of studies mainly focused on the bacterial component of microbiota in fecal samples that have shown PD-related alterations of abundance and equilibrium of gut microbiota. If an altered microbiota contributes to neurodegeneration and worsening of motor symptoms in patients with PD, a therapeutic approach with the aim to reestablish a healthy microbiota would be desirable. With all those new insights and discoveries, a lot of possible therapeutic possibilities are coming in focus: diet modifications; the administration of probiotic bacteria in order to displace pathogenic bacteria; the use of prebiotics, (nutrients metabolized by probiotic bacteria with the aim to accelerate bacterial growth); and the use of synbiotics (combination of probiotics and prebiotics). Experimental approaches such as fecal transplantation, bacterial consortium transplantation, bacteriophage therapy and the use of predatory bacteria have also been used to decrease gut inflammation.
In conclusion, current evidence suggests that abnormalities in gut microbiota may contribute to neuro-inflammation and motor progression of PD. Further studies are needed and in this lecture an overview of studies considering microbiota and PD will be presented.

Brain MRI in the diagnostic follow-up of Parkinsonism

Slavica Kovačić
University Hospital Center Rijeka, Rijeka, Croatia

The most frequently used Parkinson's disease (PD) biomarkers are the brain imaging measures of dopaminergic dysfunction using positron emission tomography and single photon emission computed tomography.
Magnetic resonance imaging is complementary method mainly for morphological changes due to MRI advantage of having a superior spatial resolution Although conventional structural imaging remains normal in PD, advanced techniques have shown changes in the substantia nigra and the cortex. The most well-developed MRI markers in PD include diffusion imaging and iron load using T2/T2* relaxometry techniques. Other quantitative biomarkers such as susceptibility-weighted imaging for iron load, magnetization transfer and ultra-high-field MRI have shown great potential. More sophisticated techniques such as tractography and resting state functional connectivity give access to anatomical and functional connectivity changes in the brain. Brain perfusion can be assessed using non-contrast-agent techniques such as arterial spin labelling and spectroscopy gives access to metabolites concentrations. MRI could support the diagnosis of PD by detecting functional changes associated with PD, such as decreased activation of motor regions by motor activating tasks, decreased white matter integrity, and metabolic changes in certain brain regions.These techniques are not standardized in clinical practice but there is great potential for application to improve the clinical diagnosis and follow- up of patients with Parkinsonism.

Can we slow down neurodegeneration in multiple sclerosis?

Gregor Brecl Jakob
University Medical Centre Ljubljana, Ljubljana, Slovenia

Multiple sclerosis (MS) is a chronic inflammatory disease limited entirely to the central nervous system (CNS)[1]. It is characterized by focal demyelinating lesions accompanied by secondary diffuse tissue damage and neurodegeneration[2]. Distinct clinical phenotypes of MS having distinct pathophysiological and pathological features exist[3-5].

In majority of the patients (85%) it begins in the third decade of life with relapses followed by remissions[3]. Studies of the natural course of the disease showed that, if left untreated, 50% of the patients will use bilateral walking aids and turn into secondary progressive stage of the disease (SP MS) after 15 years of having RR MS[6, 7]. Minority of the patients (15%) will present with insidious progression of neurological disability at the very beginning of the disease, a feature of primary progressive MS (PP MS)[3, 6].

There is still an ongoing debate about the pathophysiological background of different clinical phenotypes. An agreement exist that all pathological processes observed in MS are initially driven by primary inflammatory process. RR MS is primarily characterized by waves of autoreactive T and B lymphocytes (CD 19+) migrating into the CNS causing focal inflammatory lesions with disruption of blood brain barrier (BBB) and certain degree of axonal injury[2]. The pathology of progressive MS is similar in both forms (PP MS and SP MS) with the exception of new focal lesions and relapses being more common in SP MS. The inflammatory process is trapped within the CNS and there is little BBB disruption. Autoreactive T and B cells (plasma cells) are sequestered in the meninges and perivascular spaces forming aggregates of lymphocytes. Consequently, slowly expanding lesions and subpial cortical demyelination accompanied by diffuse damage of normal appearing white and grey matter are seen in progressive forms of MS. Axonal injury and subsequent degeneration are mediated by activation of microglia and macrophages. Oxidative stress and mitochondrial dysfunction are also considered to contribute to secondary axonal degeneration in MS[2, 8].

Fascinating progress has been made in the last three decades in the field of treatment of MS. The disease modifying therapies (DMTs) brought nearly normal life to the patients with RR.MS by modulating, suppressing or reconstituting immune system[9]. Major unmet needs remain in the treatment of progressive forms of MS, despite numerous clinical trials from the past, majority of them being negative[10]. Currently registered DMTs affecting the course of progressive MS are mostly exerting their modest effects on the disease course through suppression of the inflammatory process. The efficacy of these therapies is mostly lost in patients without disease activity (characterized by relapses or new/enlarging or contrast enhancing lesions on MRI). The effect of ocrelizumab on the course of primary progressive MS implies possible pathophysiological role of B-cells in the disability accumulation independent of relapses[11]. Siponimod, a selective S1P modulator, crosses the BBB and has potential central effects[12]. Ibudilast, an inhibitor of several cyclic nucleotide phosphodiesterases, also able to cross BBB, showed significant effect compared to placebo on brain volume loss in patients with progressive MS and RR MS, while having no effect on new lesions formation in RR MS[13]. There are other approaches such as remyelinating strategies and autologous stem cell transplantation being investigated to treat progressive forms of MS.

In conclusion, we now have a few therapeutic options to address the processes dominating progressive forms of MS, however we are far from being able to efficiently supress neurodegeneration and disability accumulation independent of relapse activity. More and more knowledge is gained each year about the possible pathophysiological mechanisms of progressive of MS allowing development of new therapeutic strategies.

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Drug development in Frontotemporal dementia

Tomislav Babic
Worldwide Clinical Trials, London, UK

Background: Although considered rare, frontotemporal dementia (FTD) represents the second most common type of early-onset dementia, predominantly affecting younger populations than Alzheimer's disease (AD) and is thought to have an even greater deleterious effect on the lives of patients and their families.
Objective: To provide a systematic review of subject selection criteria and outcome measures in Randomized Placebo Controlled Clinical Trials (RPCCT) of pharmacological interventions in FTD..
Methods: We systematically searched the electronical PubMed database for reports of RPCCT published as a full-text in English since 1990 till September 2021. Key words used were: FTD; randomized, placebo, clinical trials.
Results: A total of 15 RPCTs have been identified. All of the studies have been published within the last 18 years. Fourteen studies have used pharmacological products for the intervention, whereas one study has used a sham-controlled transcranial direct current stimulation (tDCS) as therapeutic intervention. Cross over design has used in nine studies, while parallel design has used in six studies. The 15 reviewed studies reported on a total of 676 individuals. The mean participants age from all of the studies ranged from 55.7 years to 66.3 years. The sample size ranged from 8 to 220 participants (median 26). Durations of the studies ranged from one week to 52 weeks (median = 9).
Conclusion
A huge variability among entry criteria and outcome measures have observed. All studies explored the effect on intervention on some symptoms or biomarkers. The disease modifying RPCCT was not reported.

What can we learn from the neuropathological study of corticobasal degeneration?

Tamas Revesz
UCL Queen Square Institute of Neurology
Queen Square Brain Bank for Neurological Disorders

Corticobasal degeneration (CBD) is a progressive neurodegenerative disorder characterized by accumulation of neuronal and glial inclusions, composed of hyperphosphorylated 4-repeat tau isoforms in both cortical and subcortical regions. Similar to progressive supranuclear palsy, which is also a 4-repeat tauopathy, the distribution of neuronal loss and severity of tau pathology in CBD closely correlate with its heterogeneous clinical presentations (*Kouri et al., Nature Reviews Neurology 2011;7:*263–272). Corticobasal syndrome is the classic presentation of CBD with asymmetrical focal cortical signs including limb apraxia, dystonia and akinetic-rigidity. In other cases, characteristic CBD pathology may be associated with Richardson syndrome (i.e. a PSP-like syndrome), frontotemporal dementia or primary progressive aphasia. In an earlier study from the Queen Square Brain Bank for Neurological Disorders, UCL Queen Square Institute of Neurology we showed that there is a rather poor correlation between clinical diagnosis and neuropathological diagnosis (*Ling et al. Brain 2010; 133:2045–57*).

Since January 2014 we have had the opportunity to assemble and study 124 cases, in which we could confirm the neuropathological diagnosis of CBD. In 87 cases the available clinical data allowed us to establish the clinical phenotypes, which included corticobasal syndrome (N=21), frontotemporal dementia (N=20), Richardson's syndrome (N=14), primary progressive aphasia (N=13), posterior cortical atrophy (N=1) and an overlap syndrome (N=18). Our cohort also included six cases in which the clinical presentation was 'rapidly progressive'. These patients died of clinically advanced disease within 3 years of disease onset. In this latter group our quantitative neuropathological study showed that cases had a 'total tau-load' that is comparable to that we observed in our 'end-stage' CBD cohort, which had significantly longer disease duration. Our study indicated that 'rapid progressive' CBD is a distinct aggressive variant with characteristic neuropathological substrates resulting in a fulminant disease process as evident both clinically and pathologically (*Ling et al Acta Neuropathologica 2020;139:717-34*). Investigation of our 'preclinical' cohort also provided novel data relevant for understanding disease progression in CBD, as we were able to demonstrate that the basal ganglia circuitry is the earliest neural network that is affected by CBD tau pathology, which then spreads to the dorsolateral prefrontal cortex and thence to the posterior frontal cortex (*Ling et al. Brain 2016;139:3237–52*).
It is essential to understand the neurobiological processes, including genetic factors that determine the cinicopathologial variability in CBD. Such studies are now in progress in our laboratories.

Neuroimmunity in ALS

Ivana Munitic[1], Prtenjaca Nikolina[1], Josip Peradinović[1],Hrvoje Jakovac[2] Markovinovic Andrea[3]
[1]Department of Biotechnology, University of Rijeka, Rijeka, Croatia
[2]Medical Faculty, University of Rijeka, Rijeka, Croatia
[3] King's College London, London, UK

Amyotrophic lateral sclerosis (ALS) primarily affects motor neurons and is the fastest progressing adult neurodegenerative disease. Although it is marked by remarkably broad genetic and clinical heterogeneity, one of its main hallmarks - neuroinflammation – is common to all ALS cases. Given that the immune cells are far more plastic in comparison to neurons, they are considered as attractive targets in ALS. Despite that, various anti-inflammatory approaches have either completely failed to slow down disease progression or showed very limited effects. Therefore, it is necessary to redefine the role of the immune system in neurodegeneration, and precisely distinguish its homeostatic and/or neuroprotective effects from neurotoxicity. Here we discuss multiple layers of immune-mediated neuroprotection and neurotoxicity in ALS, and address three otherwise distinct immune dysfunctions, all of which have been reported in ALS —excessive inflammation, autoimmunity and inefficient immune responses. Special focus will be on several recently characterized ALS-linked mutations, including those in TBK1, OPTN, CYLD and C9orf72, reported to lead to inefficient immune responses and/or damage pile-up, suggesting that an innate immunodeficiency may also be a trigger and/or modifier of ALS.

Clinical Neurophysiology and neurodegenerative diseases

Paolo Manganotti[1,2]
[1]University Medical Hospital of Trieste, Trieste, Italy
[2]University of Trieste, Trieste, Italy

Clinical and experimental Neurophysiology represents an usual instrument to investigate and define the amounti of degenerative changes of nervous system. EEG is a routine method important to define the brain oscillatory slowing and the progressive decrease of alpha rythms in different neurodegenerative disorders. Parkinson disaes with mild cognitive impairment are particulary rapresentative for the EEG slowing and EEG changes.
The occurrence of epilepsy in neurological degnerative disorders is often underestimated and the clinical neurophysiology is senstive and important to define the presence of epileptiform activity. Autonomic Test are mandatory in Parkinsonism as well the the investigation of pelvic floor dysnfunction.
Brain stimulation has a role to define the different motor excitability in Alzhimer dementia or in Frontotemooral dementia. Neuromodulation of brain stimulation and method of coregistration EEG and TMS are the frontiers of clinicial Neurophysiology to combine clinical and functional information. Finally the mild cognitive decline in post Covid present particular neurophysiological findings useful to understand the neurophysiological signs in neurodegnerative disorders.