

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

**6th RIJEKA FORUM ON
NEURODEGENERATIVE DISEASES**

**NEURODEGENERATION UPDATES AND
THE 30 YEARS OF AMYLOID CASCADE
HYPOTHESIS**



Endorsed by Associations
Parkinson i mi, Neurodeg and Ean



Rijeka, September 26-28, 2022
9,30 am

University Campus Rijeka, Faculty of Civil Engineering
Lecture hall G-003, Radmile Matejčić 3, Rijeka

Organizers

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Scientific Committee

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

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Vladimira Vuletić, president

Zoran Tomić, Eliša Papić, Valentino Rački, Srđan Novak

Registration: online via [registration form](#)

Free admission for registrations

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P R O G R A M
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, Assistant 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, 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

1st day – September 26th, 2022

PROGRAM

9,00 – 11,30 h

I. AMYLOID HYPOTHESIS AND RARE PARKINSONISMS

Chairmen: Zvezdan Pirtošek and Nenad Bogdanović

John Hardy, M.D., PhD, Professor, UCL Institute of Neurology, London, UK
Amyloid hypothesis... what was right and what was wrong and what should we do next?

Tamas Revesz, M.D, PhD, FRC Path, Professor Emeritus in Neuropathology, University College London UCL Queen Square Institute of Neurology, London, UK
The BRI2 gene-related dementias underpin the validity of the amyloid cascade hypothesis

Kailash Bhatia, M.D., PhD, Professor, University College London UCL Queen Square
Institute of Neurology, London, UK

An approach to Rare Parkinsonian disorders

Zvezdan Pirtošek, M.D., PhD, Professor, University Hospital Centre Ljubljana,
Ljubljana, Slovenia

Amyloid is in the eye of beholder: ophthalmological biomarkers of AD

Break for refreshment: 11:30 – 11:45

11,45 – 14,00 h

II. ALZHEIMER'S DISEASES AND MIMICRIES

Chairmen: Nenad Bogdanović and Tomislav Babić

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

Non-amyloid aging may cause Alzheimer-like dementia

Vladana Vukojević, Associate Professor, Department for Neurobiology, Caring
Science and Society, Division of Clinical Geriatrics, Karolinska Institute, Stockholm,
Sweden

**Time-resolved Thioflavin T fluorescence intensity fluctuation analysis for measuring
the concentration and size of amyloidogenic nanoplaques in blood or cerebrospinal
fluid. Potential for early diagnosis of Alzheimer's disease**

Tomislav Babić, M.D., PhD, Professor, Neuroscience Franchise Worldwide Clinical
Trials, London

**Methodology of drug development in Alzheimer's disease: What we need to
change?**

Gabriela Novotni, M.D., PhD, Associate Professor, University Clinic of Neurology,
Medical Faculty, University "Ss Cyril and Methodius", Skopje, North Macedonia

**Amyloid cascade and amyloid "confluence" hypothesis -reexploring Alzheimer's
disease(s) treatment and prevention landscape**

Nataša Klepac, M.D., PhD, Associate Professor, University Hospital Centre Zagreb,
Zagreb, Croatia

Alzheimer's disease mimicry

Elka Stefanova, M.D., PhD, Professor, Institute of Neurology CCS, School of
Medicine, University of Belgrade, Belgrade, Serbia

Frontotemporal dementia

Lunch break: 14:00 – 14:45

14,45 – 17,00 h

III. NEURODEGENERATIVE DISEASES UPDATES

Chairmen: Vladimira Vuletić and Paolo Manganotti

Paolo Manganotti, M.D., PhD, Professor, Clinical Unit of Neurology, Department of Medicine, Surgery and Health Sciences, Cattinara University Hospital ASUGI and University of Trieste, Trieste, Italy

Mild cognitive decline in long COVID-19

Vida Demarin, M.D., PhD, Professor, Academician, Head of Department of Medical Sciences of the Croatian Academy of Sciences and Arts, President of International Institute for Brain Health, Zagreb, Croatia

Circadian rhythm disruption in neurodegenerative disorders

Mario Habek, M.D., PhD, Professor, University Hospital Centre Zagreb, Zagreb, Croatia

Prodromal Autonomic Symptoms in neurological disorders

Ivana Munitić, M.D., PhD, Associate Professor, Department of Biotechnology, University of Rijeka, Croatia

Multifaceted role of optineurin in neurodegenerative diseases

2nd day – September 27th, 2022

9,00 – 14,00 h

IV. MULTIPLE SCLEROSIS

Chairmen: Robert Živadinov and David Bonifačić

Robert Živadinov, M.D., PhD, Professor, Director, Center for Biomedical Imaging at Clinical Translational Science Institute, Director, Buffalo Neuroimaging Analysis Center, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, NY

Imaging microglia in multiple sclerosis

Robert Živadinov, M.D., PhD, Professor, Director, Center for Biomedical Imaging at Clinical Translational Science Institute, Director, Buffalo Neuroimaging Analysis Center, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, NY

Imaging remyelination in multiple sclerosis

Gregor Brecl Jakob, M.D., PhD, Department of Neurology, University Medical Centre Ljubljana, Ljubljana, Slovenia
Predicting progression in Multiple sclerosis

Break for refreshment: 10:45 – 11:00

David Bonifačić, M.D., PhD, Assistant Professor, Clinical Hospital Center Rijeka, Rijeka, Croatia
Remyelination in Multiple sclerosis

Hervé Perron, PhD, GeNeuro Innovation, Lyon, France and GeNeuro SA, Geneva, Switzerland

HERV-K envelope (HERV-K ENV) neurotoxicity and detection in spinal fluid of sporadic amyotrophic lateral sclerosis: preclinical neutralization by a humanized anti-HERV-K antibody and rationale for therapeutic indication

Patrick Küry, M.D., PhD, Professor, Department of Neurology, Medical Faculty, Heinrich-Hein University of Düsseldorf, Germany

The role of HERV-W in fostering microglia dependent neurodegeneration and in preventing myelin repair in multiple sclerosis

Lunch break: 12:30 – 13:15

13,15 – 16,00 h

V. MOVEMENT DISORDERS

Chairmen: Vladimira Vuletić and Borut Peterlin

Elena Moro, M.D., PhD, President – Elect of European Academy of Neurology, Movement Disorders Unit, Director, Department of Psychiatry, Neurology, Neurological Rehabilitation and Forensic Medicine, Centre Grenoble University Hospital Center, and Grenoble Alpes University, Grenoble, France
Update on DBS for dystonia

Bettina Balint, M.D., PhD, Professor, Department of Neurology, University Hospital Zurich, University of Zurich, Zurich, Switzerland
The borderland between neurodegeneration and neuroimmunology

Borut Peterlin, M.D., PhD, Professor, University Clinical Center Ljubljana, Ljubljana, Slovenia
Genetics of neurodegenerative disorders: translation in neurology practice

Vladimira Vuletić, M.D., PhD, Assistant Professor, Clinical Hospital Center Rijeka, Rijeka
Invasive methods in advanced Parkinson's disease

Darko Chudy, MD, PhD, Professor, Department of neurosurgery, University Hospital
Dubrava, Zagreb, Croatia
DBS in patients with disorder of consciousness

Slavica Kovačić, M.D., PhD, Department of Radiology Clinical Hospital Center
Rijeka, Rijeka
Role of MRI in the modern treatment of neurodegenerative diseases

Break for refreshment: 16:00 – 16:15

16,15 – 17,15 h

**VI. DEBATE “IS ALPHA SYNUCLEIN A POTENTIAL TARGET
IN TREATING PARKINSON DISEASE”?**

Chairmen: Amos D. Korczyn and Dejan Georgiev

Dejan Georgiev, M.D., PhD, Assistant Professor, Department of Neurology,
University Medical Centre Ljubljana, Ljubljana, Slovenia
Yes

Amos D. Korczyn, M.D., PhD, Professor emeritus, CONy President Department of
Neurology, Tel Aviv University, Tel Aviv, Israel
No

3rd day – September 28th, 2022

9,00 – 10,00 h

MINI SYMPOSIUM ON PROGRESSION OF PARKINSON’S DISEASE

Chairmen: Vladimira Vuletić and Zvezdan Pirtošek

Valentino Rački, M.D., Clinical Hospital Center Rijeka, Rijeka, Croatia
Genetics and Parkinson’s disease progression

Eliša Papić, M.D., Clinical Hospital Center Rijeka, Rijeka, Croatia
Microbiota and Parkinson’s disease progression

Marina Legac Škrifić, M.D., Clinical Hospital Center Rijeka, Rijeka, Croatia
Electroencephalogram (EEG) and Parkinson’s disease progression

Anja Babić, M.D., Clinical Hospital Center Rijeka, Rijeka, Croatia
Transcranial Doppler and Parkinson’s disease progression

10,00 – 12,00 h

YOUNG RESEARCHER FORUM

Lectures TBA (chosen by Scientific Committee upon submitting abstracts)

- 1. Katina Aleksovska**
- 2. Bojana Petek**
- 3. Gaber Bergant**
- 4. Mario Hero**

12,00 – 13,00 h

POSTER SECTION

13,00 – 13,30 h

CLOSING REMARKS

Chairman: Vladimira Vuletić

Supported by HRZZ grant no. 7276

“The Epidemiology of Parkinson’s Disease in Croatia and the Influence of Genetic Factors and Microbiota on the Progression and Treatment Outcomes of the Disease”



ABSTRACTS

The Amyloid Cascade Hypothesis: what was right, what was wrong and what should we do next?

John Hardy

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

In the 1970's and 1980's, Alzheimer research was a relatively small research area. Much of the fundamental research was based on understanding the neurochemistry of the disease with the intention of trying to repeat the success of L-dopa therapy as a palliative treatment for Parkinson's disease. This research led to the current cholinergic therapy for the disease but did not address disease pathogenesis. There was little focussed research on what might cause the neuronal death in the disease: only rather vague ideas.... Accelerated ageing.... Slow viruses... aluminium..... Although pedigrees with early onset disease had been published, the disease, the general view was the disease was not genetic.

In the early 1980s, there were several important developments applying molecular biology and molecular genetics to the understanding of AD and other neurodegenerative diseases. Glenner, and Masters and Beyreuther derived the amino acid sequence of amyloid, later leading to the cloning of the APP gene and its localisation to chromosome 21, G'oert and collegus showed that tangles were made from the tau (MAPT) protein and Gusella showed in Huntington's disease that causative genes could be located by genetic linkage analysis.

On reading Gusella's paper I realised that this gene finding approach could break the Gordian knot of causation and lead to an understanding ohow the disease started.

With Martin Rossor, and with the support of Bob Williamson and with the immensely fortunate hiring o Alison Goate, we collected families with disease and, after missteps (see PMID 28054745) found mutation in amyloid which caused disease.

My view at that time was that this settled any debate about the cause of disease. Amyloid caused the disease in that family and therefore was the likely cause in all cases. The later cloning of the presenilin genes as other causes of disease by Peter Hyslop and the demonstration that these proteins were involved in cleaving amyloid from APP by De Strooper and Selkoe reinforced this view.

In parallel with Schellenberg and Spillantini, we, led by Mike Hutton showed that MAPT mutations caused tangle only dementia and this allowed us to make tangle only mice and crossing these mice with amyloid mice allowed us to show that amyloid potentiated tangle pathology but not vice versa.... experimental demonstration of the amyloid hypothesis.

However, the amyloid hypothesis was conceived of as an entirely neuronal disease and as we and others used the ever more powerful technologies of genetic analysis, we realised that the majority of genes involved in AD risk were microglial and probably involved in amyloid clearance. This has led me to alter my view and to consider a scenario

where an age-related decline in microglial function is a critical component of the disease and that, at least in part, this underlies amyloid deposition and the disease initiation. In my talk I will review these changing ideas and discuss the recent drug trials (in which I have no involvement). I remain optimistic about some benefit accruing from anti-amyloid drugs, but would not expect that eventually poly pharmacy will be the way this devastating disease is treated.

The *BRI2* gene-related dementias underpin the validity of the amyloid cascade hypothesis

Tamas Revesz

Queen Square Brain Bank for Neurological Disorders, UCL Queen Square Institute of Neurology, University College London, London, UK

The *BRI2* gene-related dementias, which currently include familial British dementia (FBD) and familial Danish dementia (FDD), are rare inherited neurodegenerative diseases caused by distinct mutations of the *BRI2* gene, broadly expressed in neurons and glial cells and, also in peripheral organs. Both mutations abolish the normal stop codon of the *BRI2* gene resulting in extended precursor proteins, post-translational processing of which releases two *de novo* created 34 amino acid-long amyloidogenic peptides, called ABri in FBD and ADan in FDD. ABri and ADan are different from one another in their twelve C-terminal amino acids. Deposition of ABri in FBD and ADan in FDD results in neuropathological phenotypes showing striking resemblance to the pathological changes seen in Alzheimer's disease (AD); as in both FBD and FDD there are cerebral parenchymal amyloid plaques, cerebral amyloid angiopathy and severe neurofibrillary tangle (NFT) pathology. Importantly, CryoEM studies have demonstrated that the atomic model of the tau filaments composing NFTs in FBD, FDD and AD is identical. Similar to the AD-associated A β peptide, ABri and ADan are neurotoxic; e.g. they can elicit a marked astrocytic and activated microglial response and activate both the classical and alternative complement pathways.

Conclusions: Although the ABri and ADan amyloid peptides show no amino acid sequence homology with the A β peptide, these three amyloid forming peptides can be considered molecular equivalents in that they are able to trigger analogous cascades of pathogenic events resulting in severe neurodegeneration and neuropathological manifestations.

Amyloid is in the eye of beholder: ophthalmological biomarkers of AD

Zvezdan Pirtošek

University Hospital Centre Ljubljana, Ljubljana, Slovenia

As determination of the imaging and CSF biomarkers is expensive and invasive, intensive research work is ongoing in this area. The eye, which on the one hand is a peripheral, easily accessible organ, with the retina being the only physiological 'window' of the CNS, offers several possible biomarkers for early diagnosis, for monitoring of the disease progression and for assessing therapeutic effectiveness.

There is almost no part of the eye that has not been studied for these purposes in neurodegenerative diseases with increasingly sophisticated methods. Studies of prot-

omics in **tears** reported: 1) that 4 proteins (lipocalin-1, dermicidin, lysozyme C, and lactricin) have a sensitivity of 81% and a specificity of 77% in the diagnosis of AD; 2) that total microRNA and the most promising mRNA-200b-5p are elevated in AD and 3) that a biosensor that detects A β in tears is being developed (3). In the **cornea**, morphological changes of blood vessels have been described in patients with AD (4). In the **pupil**, a reduced latency and amplitude of the pupillary reflex to illumination during a cognitive task and an atypical response to cholinergic antagonists were found (5). Pathological proteins have been detected in the **lens** (5). Light neurofilament was found in the **vitreous body** in AD; an important component of the axon, used to demonstrate the process of neurodegeneration and to distinguish between individual types of dementia (e.g. AD and frontotemporal) (6). The **choroid** is thinned (5). The **retina** was studied using the methods of optical coherence tomography and optical coherence tomography angiography. Retinal venous flow is reduced (5), A β and tau protein deposits (7), ganglion cell degeneration (5) and thinning of the ganglion cell and retinal nerve fiber layer are seen (5). The **optic nerve** head is paler with a reduced amount of axonal projections (8). With the method of confocal scanning laser tomography, alpha synuclein deposits were demonstrated in patients with Parkinson's disease (9) and it is only a matter of time when a similar study will be performed in patients with AB with the aim of detecting A β , which has been accumulating in the brain for years before the first clinical signs.

Just recently, some important works have appeared that indicate the great potential of the eye for the early detection of neurodegenerative diseases. Thus, Yoon et al. studied 70 eyes (39 patients with AD, 72 eyes (37 patients) with mild cognitive impairment (MCI) and 254 eyes of 133 healthy volunteers using optical coherence tomography angiography (10). Compared to MCI and healthy volunteers, patients had lower macular vascular density, poorer perfusion, thinner ganglion cell layer and inner plexiform area (GC-IPL), while retinal microvascular changes were the same as those in the brain of AD patients (10). An excellent literature review and meta-analysis on ocular biomarkers was published by Ge et al (11).

References:

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10. Yoon, S. P., Grewal, D. S., Thompson, A. C., Polascik, B. W., Dunn, C., Burke, J. R., et al. *Ophthalmol. Retin.* 2019 (3), 489–499;
11. Ge Yi Yun et al. *Ageing Research Reviews*, 2021 (69): 101361.

Non-amyloid aging may cause Alzheimer-like dementia

Nenad Bogdanović^{1,2}

¹Karolinska University Hospital, Stockholm, Sweden

²Karolinska Institute, Stockholm, Sweden

One of the characteristic morphological features in the aging brain is the accumulation of tau protein in the limbic region, especially in the hippocampus. Higher medial temporal lobe tau was related to higher age in the subjects without evidence of amyloid. Among temporal lobe subregions, episodic memory was most strongly related to tau accumulation in the entorhinal region. Our data are consistent with neuropathological studies and further suggest that entorhinal tau pathology underlies memory decline in old age even without amyloid. The group of patients older than 65 but specifically over 80 years who display normal cognition or mild cognitive impairment are amyloid-negative but neurodegeneration-positive by means of CSF and MRI biomarker and neuropsychological testing. Since a clinical picture can mimic an early AD these patients can get the wrong diagnosis of AD and get the wrong treatment if biomarker analysis is not performed. Thanks to the biomarker signature a concept of suspected non-Alzheimer disease pathophysiology (SNAP) has been introduced. SNAP is present in ~23% of clinically normal individuals aged >65 years and in ~25% of mildly cognitively impaired individuals. *APOE4* is underrepresented in individuals with SNAP compared with amyloid-positive individuals which further implies the lack of amyloid in these initial phases. Individuals with SNAP changes and still normal cognition or mild cognitive impairment have worse clinical and/or cognitive outcomes than individuals with normal levels of neurodegeneration and amyloid- β biomarkers. SNAP was first described in a study in which the National Institute on Aging–Alzheimer’s Association (NIA–AA) criteria of preclinical AD were examined.

The patterns of atrophy and hypometabolism in non-AD conditions often overlap spatially with the patterns seen in AD. This is the most obvious in the medial temporal lobe. Hippocampal atrophy is not the early feature only in AD but it can be seen in hippocampal sclerosis, TDP-43 pathology (LATE), anoxic–ischemic injury, and Primary Age-Related Tauopathy (PART) such as argyrophilic grain disease, tangle only dementia. Even hypometabolism is found in non-AD conditions similar as in AD with the predominant temporoparietal pattern of decreased glucose uptake, indicating that the AD-like hypometabolism in posterior association areas that is observed in PART can be explained by the fact that these areas are highly connected, both structurally and functionally, to the medial temporal lobe. This indicates that networks in these areas can be vulnerable to a variety of insults associated with AD, non-AD disorders, and aging. PART is almost universally detectable at autopsy among elderly individuals, yet this pathological process cannot be easily identified pre-mortem at present despite the that some specific clinical features during the diagnostic procedure could be indicative to non-AD pathology. This specific concept is still under development, but several important steps are made in understanding the differential diagnostic picture of dementia of 80+ individuals suffering from PART. It is important that every practitioner is aware of this extremely common pathologic change (SNAP/PART etiology) since the final diagnosis and therapy may differ from AD or mixed AD. Cognitive impairment is often mild, and recent studies have identified a common biomarker profile consisting of specific temporal lobe atrophy and tauopathy without evidence of $A\beta$ accumulation.

MRI can reveal asymmetric involvement of the hippocampal atrophy characteristic for both AD and PART but unlike in typical Alzheimer's disease where atrophy of the hippocampus does not show an anterior and posterior gradient, atrophy in definite PART showed an anterior and left-side predominance. This observation is important for clinical use since there is evidence that the anterior and posterior hippocampus have different network connections with the posterior hippocampus involved with retrieval and encoding aspects of episodic memory. The lack of posterior hippocampal degeneration can be neuropsychologically tested which may suggest different neurodegeneration, accordingly suggesting the clinical difference between AD and PART. Similarly, in semantic dementia involvement of the anterior hippocampus is the MRI hallmark of this dementia which is characterized by relative sparing of episodic memory, and hence it would not be surprising for PART to be associated with the semantic dementia-like phenotype. While PART and SD may have some MRI similarities the entire clinical and neuropsychological phenotype, age of onset, and additional anatomical changes clearly differentiate between these two neurodegenerative entities (Figure 1.) Moreover, PART differs from AD, by the low frequency of the APOE 4 allele. The frequency of the APOE4 allele in AD is 3–4 times higher than in definite PART. It is known that the APOE4, has been linked to the accumulation of beta-amyloid hence PART has less or no amyloid pathology so typical for classical AD. Thus, PART has cognitive consequences that should be considered in the context of emerging therapies targeting tau in age-associated neurodegenerative diseases. Neurobiologically hippocampal formation is specifically vulnerable to tau in the aging brain which is a morphological substrate of age-related episodic-memory loss and dementia of old age. In summary, the clinical feature of SNAP/PART is separate from AD and its distinction is enormously important for the clinical management of patients with cognitive impairment and for public health care planning.

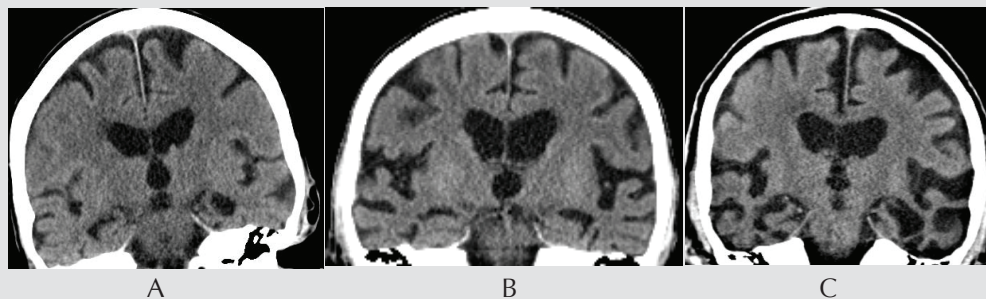


Fig 1. CT coronary images at the level of the anterior hippocampus in a patient with PART (A), late-onset Alzheimer's Disease (B), and Primary Progressive fluent Aphasia – Semantic Dementia (C). Note predominant left > right anterior hippocampus atrophy in all three patients which should not be related to Alzheimer's Disease only. Patient A – Part is 85 y old, MMT 23/30, APOE 2/3 and normal CSF biomarkers, clinically predominant amnesic cognitive impairments, and mild dementia. Patient B – late-onset AD, APOE 4/3, CSF biomarkers for AD, MMT 20/30, clinical primary amnesic cognitive impairment and mild dementia, besides MTL atrophy mild/moderate cortical atrophy, Patient C – moderate advanced Semantic dementia in 75 y patient with characteristic severe atrophy of the left MTL and temporal pole that has spread

towards opposite temporal lobe and left frontal cortex, normal CSF biomarkers, APOE 3/2, MMT 19/30, clinical progressive fluent aphasia as a part of FTLD. Awareness of pathognomonic atrophy of fusiform gyrus (white arrow) can indicate Semantic Dementia in the very early stage of this disease. Without the use of biomarkers and careful image analysis patient A and C are commonly misdiagnosed with Alzheimer's Disease which use to have vast consequences in post-diagnosed management of those phenotypes.

Time-resolved Thioflavin T fluorescence intensity fluctuation analysis for measuring the concentration and size of amyloidogenic nanoplaques in blood or cerebrospinal fluid. Potential for early diagnosis of Alzheimer's disease

Ann Tiiman¹, Vesna Jelić², Jüri Jarvet³, Sebastian Wärmländer³, Rudolf Rigler⁴, Lars Terenius¹, Astrid Gräslund³, Nenad Bogdanović^{1,2}, Vladana Vukojević^{1*}

¹Center for Molecular Medicine, Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden

²Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society (NVS), Karolinska Institute, Stockholm, Sweden

³Arrhenius Laboratories, Department of Biochemistry and Biophysics, Stockholm University, Stockholm, Sweden

A novel, time-resolved FCS (fluorescence correlation spectroscopy)-based method with single-molecule sensitivity was recently developed and used to measure the concentration and size of Thioflavin T (ThT)-active protein aggregates enriched with pleated β -sheet secondary structure, so-called amyloidogenic nanoplaques, in the serum and cerebrospinal fluid (CSF) of healthy individuals or individuals with Alzheimer's disease¹⁻⁵. In this method, described in detail I Tiiman *et al.* 2019¹, the amyloid-specific fluorescent dye ThT, from which several amyloid-PET (Positron Emission Tomography) probes were derived, is used to render fluorescent amyloidogenic nanoplaques, while the minute observation volume ($\sim 0.2 \times 10^{-15} \text{ dm}^3$), high (sub-microsecond) temporal resolution and single-photon detection sensitivity of avalanche photodiodes (APDs), enables us to detect suspended (not precipitated) amyloidogenic nanoplaques with the ultimate, single-molecule sensitivity, and allows us to measure their concentration and size¹. We present this method and results obtained by serum and CSF analysis in healthy individuals and patients in naturalistic memory clinic cohorts and discuss its potential for early Alzheimer's disease (AD) diagnosis, following AD progression, and for monitoring the therapeutic efficacy of treatments aiming to reduce the amyloidogenic load.

References:

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Methodology of drug development in Alzheimer's disease: What we need to change?

Tomislav Babić

Neuroscience Franchises Worldwide Clinical Trials, London, UK

Alzheimer's disease (AD) is a progressive degenerative disorder of cognitive functions followed by behavioral and personality changes, which significantly affect quality of patient's and caregiver's life, progressively reducing patient's activity of daily living (ADL) until complete dependence on external care.

In spite of, a clear need for treatments that could slow or stop the progression of AD, such treatment is still not available. A symptomatic treatment with acetyl-cholinesterase inhibitors and memantine, introduced in clinical practice more than 20 years ago, are still the only approved treatment with humble effect. Although FDA recently approved aducanumab for the treatment of AD, the genesis and story behind is so bizarre and it is hardly to believe that aducanumab will improve medical care of AD at all.

Numerous confirmatory clinical trials (symptomatic or disease modifying) have been launched during the last 20 years, but there has been no completed trial with statistically significant or clinically meaningful outcomes in favor of the test drug. Although this is most likely due to the inefficacy of the drugs tested and underpowered trials, other possibilities include the insensitivity of the cognitive, global, and activities of daily living outcome measures, incorrect assumptions regarding underlying pathology and clinical course, or inappropriate medical management of clinical trial.

In a progressive condition like AD, therapeutic benefit with an active drug can be represented as an improvement in a score on a particular test, by stabilization on the test, or by less than expected decline, all by comparison with the placebo-treated control group. Therefore, the expected decline on placebo, which is, in fact, representing a natural course of cognitive decline in AD is a very important element within the clinical trial. Error components, added to clinical ratings by inaccuracies, imprecision, failures to follow or lack of operational protocols for applying methods, and bias, have been shown to decrease active drug-placebo group differences and to increase the variance in data. These effects on data reduce the possibilities for reaching statistical significance for outcome measure differences.

Similar measurement errors and a lack of specificity during diagnostic evaluations and qualifications of subjects for eligibility for clinical trials can include subjects incapable of responding to treatment because of misdiagnosis, genetics, or specific pathology.

Each of these factors reduces the power of the clinical trial to detect drug-placebo

differences; requiring additional subjects, additional sites to provide subjects, more investment in training investigators, risk of recruiting clinically inexperienced investigators, increased resources for monitoring sites thus contributing further risks of compromising the integrity of the clinical trials.

On the other side, the pressure to recruit faster and faster more patients increases the exposure to situations where some subjects are not fully congruent with protocol. The speed kills not only on the road, it killed a lot of molecules in clinical trials in AD.

Amyloid cascade and amyloid “confluence” hypothesis -reexploring Alzheimer’s disease(s) treatment and prevention landscape

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On the 30th anniversary of the “amyloid cascade hypothesis” that has largely influenced drug development pipeline for the disease described 115years ago and still in need of a cure, it is time to ask questions and reexplore the diversity of mechanisms and multiple pathogenic pathways involved in the complex pathophysiology of Alzheimer’s disease (AD).

The role and central position of amyloid proposed by the “cascade hypothesis” is not questioned, but the “cascade” itself, as it is mostly applicable for and initially originated from the evidence in the autosomal dominant AD. When discussing the etiology and pathogenesis of the more frequent, sporadic AD, amyloid too has the central position, but the overall disease pathogenesis is rather in a “confluence” than in a “cascade” manner, talking in “river terminology”. This talk is inspired by the recently suggested “probabilistic model of Alzheimer’s disease”, shifting the understanding of AD pathophysiology from a deterministic model suggested by the “amyloid cascade hypothesis” to a probabilistic model where stochastic factors play relevant role.

In sporadic AD, heterogeneous factors and mechanisms in variable proportion and extent are involved in the pathogenesis of the disease (genetic, vascular and lifestyle risk factors, APOE e4 related neurobiological mechanisms, neuroinflammation etc.). This complex interplay can schematically be presented as multiple streams forming multiple junctions flowing together to a point of reaching the threshold -the “confluence” that leads to a disease.

Alzheimer’s disease is a polygenic, multifactorial disease or even better a syndrome, thus a single pathway targeted treatment is unlikely to work. It might be wiser to use Alzheimer’s disease as an umbrella term, or Alzheimer’s diseases or discuss on different AD variants (at least three, autosomal dominant AD, APOE e4 -related sporadic AD and APOE e4 - unrelated sporadic AD, as suggested by the “probabilistic model”). Different models and hypothesis might just be different parts of a much bigger picture simply named as “the pathophysiology of AD”, a process that as a whole and in details is still unknown to us. These hypotheses are not opposed to one another but use different points of view.

Looking from the perspective of the probabilistic model, a broader treatment and prevention frame is emerging. Personalized approach in risk profiling and identifying the

dominant pathogenic pathways early in the disease process, might offer an individually tailored multiple-pathways targeted treatment and lifestyle interventions that would eventually stop multiple streams from flowing together and forming the “confluence”.

Alzheimer’s disease mimicry

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Alzheimer’s disease (AD) is the most common cause of cognitive impairment or dementia in individuals older than 65 years and, with rising longevity, a worldwide pandemic of is anticipated. Symptoms too often go undiagnosed, misattributed, or dismissed and ignored, which causes distressing, costly, and potentially harmful delays in receiving appropriate care. Due to high incidence of AD timely detection, accurate diagnosis, and appropriate management are imperative. The high prior likelihood that an elderly individual with cognitive impairment has AD should not preclude consideration of other causes. AD generally presents as a slowly progressive amnesic syndrome in later life. Beyond this typical amnesic AD profile, several atypical presentations of AD have been described and account for about 6–14% of AD cases. There are several conditions that can mimic AD. It is always important to consider ‘reversible’ or treatable conditions since the correction of underlying deficit can cure the patient. AD can also mimic a range of other conditions. Main differential diagnoses include hippocampal sclerosis with TDP-43, primary age-related tauopathy, argyrophilic grain disease, frontotemporal lobar degeneration, Lewy body disease, chronic traumatic encephalopathy as well as nondegenerative disorders such as cerebrovascular disease, chronic alcohol consumption, limbic encephalitis, medial temporal lobe epilepsy, and others. Aside from endogenous variation in the AD phenotype, a further issue (particularly in older patients) is the real possibility of mixed pathology, eg, superadded vascular damage or Lewy body pathology, which may modify the AD phenotype. AD-related pathological changes often coexist with 1 or more other pathologies, particularly vascular-ischemic cerebral injury, and diffuse Lewy body (DLB) disease. In many cases AD can be accurately diagnosed by a comprehensive evaluation that integrates careful history taking, standard investigations including pathologic AD biomarkers (cerebrospinal fluid [CSF] and amyloid PET). AD biomarkers, particularly MRI and neuropsychology—can help to define atypical or unusual cases and can be very useful in assessing the likelihood of AD versus other conditions. This is complicated by the presence of multiple pathologies and the absence of reliable biomarkers for most other causes

AD and its variants continue to challenge the physician, with the ever-diversifying neurodegenerative disease which can mimic AD. Research on neuroimaging or biological biomarkers should help disentangle these diseases in the future. This situation will, however, be transformed by the advent of targeted disease modifying therapies with the potential for substantial benefit. This prospect lends impetus to the search for new and robust in vivo biomarkers of AD pathology that can improve an early diagnosis of AD.

Mild cognitive decline in long COVID-19

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“Long-COVID” is a clinical entity that consists of persisting post-infectious symptoms that last for more than three months after the onset of the first acute COVID-19 symptoms. Among these, a cluster of neurological persisting symptoms defines Neuro-Long-COVID. While the debate about the pathogenesis of Long-COVID is still ongoing, sex differences have been individuated for both the acute and the chronic stage of the infection. We conducted a retrospective study describing sex differences in a large sample of patients with Neuro-Long-COVID. Demographic and clinical data were collected in a specifically designed Neuro-Long-Covid outpatient service. Our sample included 213 patients: 151 were females and 62 were males; the mean age was similar between females (53 y, standard deviation 14) and males (55 y, standard deviation 15); no significant differences were present between the demographic features across the two groups. Despite the prevalence of the specific chronic symptoms between male and females showed no significant differences, the total number of females accessing our service was higher than that of males, confirming the higher prevalence of Neuro-Long-COVID in female individuals. Conversely, a worse acute phase response in males rather than females was confirmed by a significant difference in the rates of acute respiratory symptoms ($p = 0.008$), dyspnea ($p = 0.018$), respiratory failure ($p = 0.010$) and the consequent need for ventilation ($p = 0.015$), together with other acute symptoms such as palpitations ($p = 0.049$), headache ($p = 0.001$) and joint pain ($p = 0.049$). Taken together, these findings offer a subgroup analysis based on sex-dependent characteristics, which can support a tailored-medicine approach. Attention, working memory and executive processing have been reported to be consistently impaired in Neuro-Long-Covid. On the hypothesis of abnormal cortical excitability, we investigated the functional state of inhibitory and excitatory cortical regulatory circuits by single and paired pulse transcranial magnetic stimulation (TMS)

In a small group of 18 patients who referred to our Neuro-Long-Covid with persistent cognitive impairment after months we compared clinical symptoms and neurophysiological investigations. The mean age of the patients and the HC were 55 years (standard deviation 10,93 years) and 27,73 years (1,75 years standard deviation), respectively. Patients were evaluated by Montreal Cognitive Assessment (MoCA) and with the Fatigue Severity Scale (FSS) was compiled by 72% (13/18) of the patients. Seventy-seven % (14/18) of the patients underwent a full neuropsychological evaluation. We performed TMS of the motor (M1) cortex in all the patients and the HC, evaluating resting motor threshold (RMT), median amplitude of the motor evoked potential (MEP), short intra-cortical inhibition (SICI), intra-cortical facilitation (ICF) and long intra-cortical inhibition (LICI) in all the subjects. Short-afferent inhibition (SAI) was investigated in all the Neuro-Long-COVID patients.

Results: The patients reported a mean number of 3,14 (standard deviation 1,70) symptoms persisting at least twelve weeks after the onset of the first symptoms of the infection. The three most prevalent symptoms were defect of attention and working memory and executive processing. The patients’ mean MoCA score was 25,52 (2,16 standard deviation). Eighty-three % of the patients (15/18) showed some impairment either in

the executive sub-item of the MoCA or in the neuropsychological assessment. The majority (77 %) of the patients reported high levels of perceived fatigue in the FSS (mean 5,61, standard deviation 1,63). (*stringere*)

The RMT and baseline MEPs of the patients and the HC were comparable ($p=0,771$ and $p=0,888$, respectively). Compared to HC, the patients showed a reduced amount of inhibition in IICI ($p=0,025$), reflecting an alteration of GABA_B regulation. SICI, ICF and SAI were not found to be significantly different between the two groups. suggesting that glutamatergic and cholinergic regulatory circuits are not impaired in Neuro-Long-Covid.

Conclusion: Neuro-Long-COVID patients with dysexecutive syndrome presented a reduction of long intracortical inhibition and glutamatergic related to GABA_B inhibition circuits that might functionally underlie and connected with such cognitive impairment.

Circadian rhythm disruption in neurodegenerative disorders

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Epigenetic factors and major stresses from different types of stimuli acting through distinct pathways and neurotransmitters are highly involved in altering the psychoneuroendocrinoimmunology (PNEI) axis, resulting in the emergence of disease. PNEI approach is a complex and multifactorial and circadian rhythm and its disruption is one of the major factors in need of a special attention.

Disturbance of the circadian system, manifested as disrupted daily rhythms of physiologic parameters such as sleep, activity, and hormone secretion has long been observed as a symptom of several neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington disease etc. Patients with various neurodegenerative diseases often show problems with circadian clocks even years before other symptoms develop.

While circadian disruptions are often considered to be symptoms of neurodegenerative diseases, recent evidence has shown that circadian disruptions (CDs) can often precede onset of other neurodegenerative symptoms in several types of neurodegenerative disorders (ND) patients by years. This has caused researchers to look at circadian rhythm disruptions in a different light: rather than being just a symptom of ND, perhaps CDs play a more active role in the origin of the diseases, as their connection is obviously bidirectional. While circadian rhythms are responsible for the timing of the sleep-wake cycle, disruptions in circadian rhythms are distinct from disruptions in sleep. The two can be distinguished by circadian rhythm biomarkers such as melatonin. There are also sleep disorders that are not a result of any differences in circadian rhythms.

Sleep and circadian rhythms are interconnected and all-encompassing physiological systems that affect virtually all biological functions. Unsurprisingly, circadian disruption can precipitate considerable impairments on human health. In neurodegenerative diseases, although it is well established that sleep and circadian dysfunctions are both a consequence of and a causal factor of neurodegenerative processes, the integrative investigation of clocks, sleep and neurodegeneration is still in its beginning. The extent of neuropathological dysfunctions in sleep and circadian neural centers is still not fully understood. The accelerating progress in this field is holding promising insights into the development of efficient therapies for improving health condition in patients

with neurodegenerative diseases. Chronotherapies such as the use of timed bright light therapy is a recent example of how fundamental research in this field have yielded positive outcomes in patients with neurodegenerative disorders. Further studies in this particular field are warranted.

Multifaceted role of optineurin in neurodegenerative diseases

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Protein aggregation, mitochondrial dysfunction and neuroinflammation are common pathogenic hallmarks of neurodegenerative diseases. A ubiquitin-binding adaptor protein optineurin has been implicated in several pathways linked to neurodegeneration including autophagy-mediated degradation of protein aggregates and damaged mitochondria, and inflammatory signaling. Notably, optineurin mutations, together with mutations of its key interacting partners, TANK binding kinase 1 (TBK1) and p62/sequestosome-1, have been found in patients with amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), neurodegenerative diseases affecting primarily motor and cognitive functions, respectively. Mutations in optineurin and TBK1 are also linked to primary open angle glaucoma, a neurodegenerative disease targeting retinal ganglion cells. In this lecture, I will compare the optineurin mutations found in different neurodegenerative diseases and discuss their effects on autophagy and inflammation.

Imaging Microglia in multiple sclerosis

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The treatment of multiple sclerosis (MS) has been transformed by the successful development of immunotherapies that efficiently reduce disease activity. Nevertheless, the prevention of disability progression is therapeutically challenging, particularly during the progressive phase of the disease. Microglia and CNS-infiltrating macrophages play significant roles in the pathogenesis of neuroinflammatory and neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis. Prolonged and dysregulated inflammatory responses by these innate immune cells can have deleterious effects on the surrounding CNS microenvironment, which can worsen neurodegeneration and demyelination. However, although chronic activation of pro-inflammatory microglia is maladaptive, other functional microglial subtypes play beneficial roles during CNS repair and regeneration. Therefore, there is a tremendous interest in understanding the underlying mechanism of the activation of these reparative/regenerative microglia. Trials of potential agents regulating microglia activity are becoming more important in the spectrum of MS research. Inhibitors of Bruton's tyrosine kinase, for which there are currently eleven Phase 3 clinical trials in MS, are postulated to affect microglia. However, adequate imaging outcomes are required that are sensitive and specific to microglia, while also being reproducible and clinically meaningful. Unfortunately, the conventional MRI sequences have limited specificity.

This lecture will evaluate the imaging modalities which are potentially more specific to detecting microglia activation at magnetic resonance imaging (MRI) and positron emission tomography (PET) imaging. At present, MRI measures, like slowly expanding lesions, probably offer the most realistic and feasible outcome measures for such trials, especially in the brain. PET may be less feasible for current and near-future trials, but is a promising technique because of its specificity. Animal studies have provided targets for interventions, paving the way for the translation of this research to humans.

Study conflict: None.

Disclosures: Robert Zivadinov received personal compensation from Novartis, Sanofi, Bristol Myers Squibb, Keystone Heart, Protembis, 415 Capital, Pixel, 3D Communications, Janssen and EMD Serono for speaking and consultant fees. Dr. Zivadinov received financial support for research activities from Novartis, Sanofi, Bristol Myers Squibb, Protembis, CorEvitax, Mapi Pharma and V-WAVE Medical.

Imaging Remyelination in multiple sclerosis

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The strategies to counteract neurodegeneration in multiple sclerosis (MS) include neuroprotection by enhancing myelin regeneration and repair, nerve conduction restoration and metabolic support of the axon. Trials of potential neuroreparative agents are becoming more important in the spectrum of MS research. However, adequate imaging outcomes are required that are sensitive and specific to myelin, while also being reproducible and clinically meaningful. Unfortunately, the conventional MRI sequences have limited specificity for myelination.

This lecture will evaluate the imaging modalities which are potentially more specific to myelin content in vivo, such as magnetization transfer ratio (MTR), myelin water fraction and diffusion tensor imaging (DTI) metrics, in addition to positron emission tomography (PET) imaging. Although most imaging applications to date have focused on the brain, we will consider measures with the potential to detect remyelination in the spinal cord and in the optic nerve. At present, MTR and DTI measures probably offer the most realistic and feasible outcome measures for such trials, especially in the brain. PET may be less feasible for current and near-future trials, but is a promising technique because of its specificity. In the optic nerve, visual evoked potentials can indicate demyelination and should be correlated with an imaging outcome. Animal studies have provided targets for interventions to improve brain and spinal cord remyelination, paving the way for the translation of this research to humans.

Study conflict: None.

Disclosures: Robert Zivadinov received personal compensation from Novartis, Sanofi, Bristol Myers Squibb, Keystone Heart, Protembis, 415 Capital, Pixel, 3D Communications, Janssen and EMD Serono for speaking and consultant fees. Dr. Zivadinov received financial support for research activities from Novartis, Sanofi, Bristol Myers Squibb, Protembis, CorEvitax, Mapi Pharma and V-WAVE Medical.

Predicting progression in multiple sclerosis

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Multiple sclerosis is a chronic autoimmune inflammatory demyelinating and neurodegenerative disease having variable course in each patient.¹ Observing the clinical course of different patients a few patterns can be depicted. Most commonly patients present with relapses followed by remissions having relapsing remitting MS (RR MS). Minority (around 15%) of the patients have progressive course (primary progressive MS – PP MS) and slowly accumulate neurological disability from the beginning of the disease. RR MS may turn into secondary progressive MS, which represents a bad prognostic factor for disability accumulation in the future². If left untreated around 50 % of the patients with RR MS will need bilateral assistance to walk and similarly 50 % will turn into the SP MS in the first 15 years from disease onset³. The prognosis of PP MS might be even worse with median time to EDSS 6 of 8 years⁴.

Recently, multiple therapeutic options available primarily for RR MS but also for PP MS and SP MS having different efficacy and safety profiles become available. Therefore, individualized treatment decisions are needed in order to properly choose the best therapeutic option for the patient emphasizing the importance of the use of reliable prognostic markers in everyday clinical practice.

Traditionally, clinical parameters from the natural disease course studies predicting worse outcomes were used in everyday clinical practice. Later MRI and laboratory measures were validated. Recently, new methods using machine learning algorithms are being developed with a goal to precisely predict future disability accumulation in a specific patient. Demographic and patients related features associated with poor clinical outcomes in RR MS are older age at onset, male sex, Black/Hispanic race, cardiovascular comorbidities, psychiatric comorbidities and smoking⁵.

Certain clinical features related to the disease course in the first years are also predictive of future disability accumulation. Higher relapse rates, poor recovery from the first relapse, pyramidal, cerebellar, sphincteric, cognitive or multifocal symptoms at onset and rapid accumulation of disability are all considered bad prognostic factors⁶. Certain features on MRI, such as rapid accumulation of new T2 lesions, Gadolinium-enhancing lesions at baseline, infratentorial lesions or spinal cord lesions at baseline, also predict poor clinical outcome. Recently, new methods such as whole brain atrophy, spinal cord atrophy and thalamic volume were shown to be predictive of future disability. Later, are however, at the moment of limited use in everyday clinical practice due to lack of availability of specific MRI sequences, automatic MRI quantification and validation⁵. Most widely used and well validated laboratory biomarker to predict poorer outcomes in patients with RR MS is the presence of oligoclonal bands in CSF. Neurofilaments in CSF and/or blood are also linked to poorer outcomes, however are not widely used due to low accessibility, high costs and lack of validation⁵.

Less is known about predicting disability progression in patients with PP MS. Rapid accumulation of disability at the beginning of the disease and development of new T2 lesions on MRI are related to poorer outcomes⁷. Advanced MRI techniques such as grey matter atrophy measures and spinal cord atrophy also predict future disability accumulation, however these measures lack clinical validation and are of limited use at the moment for the same reasons as in RR MS^{8,9}.

To conclude, we now have plenty of independent biomarkers to predict poor prognosis in patients with MS, however we still lack a method or a model of combining these and new biomarkers to better predict outcomes in a specific patient.

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Remyelination in multiple sclerosis

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Multiple sclerosis (MS) is a complex disease of the central nervous system, characterized by inflammation, demyelination, neuroaxon loss and gliosis. Inflammatory demyelinating lesions are a hallmark of the disease, however, spontaneous remyelination is often incomplete and requires strategies to stimulate it with the necessary precise and sensitive *in vivo* measurements of remyelination.

Despite significant diagnostic and therapeutic advances, which lead to a reduction in the number of disease recurrences, and accordingly to an improvement in the quality of life of patients, the prevention of long-term progression of disability is still an unreach goal. At the same time, the necessity of developing therapeutic strategies aimed at the recovery of demyelinated lesions and protection of axons from degeneration should be emphasized. The ability of the human brain to self-regenerate a demyelinated lesion has opened up a field of research aimed at stimulating this endogenous potential, and by setting the therapeutic targets of remyelination, we are opening an active field of MS treatment approaches.

With the development of the disease, chronically demyelinated axons become susceptible to degeneration due to the loss of trophic support by oligodendrocytes and myelin, forming the basic process of disability progression in multiple sclerosis. Encouraging remyelination is a promising neuroprotective therapeutic strategy, but to date it has not been achieved by simply promoting the differentiation of oligodendrocyte precursor cells, and it is clear that a detailed understanding of the molecular mechanisms underlying failed remyelination is needed to guide future therapeutic approaches. In multiple sclerosis, remyelination is weakened by external inhibitory signals in the microenvironment of the lesion and internal defects in cells of the oligodendrocyte lineage, mostly by increased metabolic demands that cause oxidative stress and accelerated cell aging induced by stress. Promising progress in our understanding of the cellular and molecular mechanisms underlying the aforementioned processes offers future strategically designed treatments with the aim of remyelination, which may present clinical improvement of the disease. Although stimulating remyelination with heterogeneous efficacy is still in the early stages of testing, the results open the door to a new approach to the treatment of multiple sclerosis.

HERV-K envelope (HERV-K ENV) neurotoxicity and detection in spinal fluid of sporadic amyotrophic lateral sclerosis: preclinical neutralization by a humanized anti-HERV-K antibody and rationale for therapeutic indication

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Human Endogenous Retroviruses have been implicated in neurodegenerative diseases (Kury et al., 2018), including amyotrophic lateral sclerosis (ALS). Expression of human endogenous retrovirus K (HERV-K) envelope (Env) in human neuronal cultures and in transgenic mice results in neurotoxicity and neurodegeneration and mice expressing HERV-K Env display behavioral and neuromuscular characteristics resembling ALS (Li et al., 2015). We have presently studied and shown Env neurotoxicity using recombinant Env protein in a cell-based assay and a mouse model. The mechanism of neurotoxicity was assessed with immunoprecipitation followed by mass spectrometry and Western blot, and by screening a panel of inhibitors. We observed that recombinant HERV-K Env protein caused neurotoxicity resulting in neuronal cell death, retraction of neurites, and decreased neuronal electrical activity. Injection of the HERV-K Env protein into the brains of mice also resulted in neuronal cell death. HERV-K Env protein was also found in the cerebrospinal fluid patients with sporadic ALS. The neurotoxic properties of HERV-K Env in sporadic ALS CSF could be rescued with both murine and humanized anti-Env monoclonal antibody. HERV-K Env was found to bind to CD98HC complexed to $\beta 1$ integrin.

In conclusion HERV-K Env is released extracellularly in sporadic ALS and causes neurotoxicity via a novel mechanism. Present results pave the way for new treatment strategies in sporadic ALS, which could be provided by the newly humanized antibody that was shown to neutralize HERV-K ENV neurotoxicity in ALS CSF.

Key words: Amyotrophic lateral sclerosis (ALS); neurotoxicity; Human endogenous retrovirus (HERV); HERV-K envelope; CSF; therapeutic antibody

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The role of HERV-W in fostering microglia dependent neurodegeneration and in preventing myelin repair in MS

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Human endogenous retroviruses (HERVs) originate from mammalian germ-line retroviral infections millions of years ago. HERVs, particularly the HERV-W subtype, have repetitively been shown to be activated in multiple sclerosis (MS) patients and to be implicated in different disease associated processes. We investigated HERV-W pathological roles related to smoldering neurodegeneration as well as in preventing intrinsic repair processes aiming at restoring damaged myelin sheaths. We could demonstrate *ex vivo* that the activity of oligodendroglial precursor cells (OPCs) to mature and generate new myelin sheaths around denuded axons was severely diminished upon contact with HERV-W ENV protein. Based on the observed proximity between ENV protein and OPCs in the vicinity of MS lesions it is therefore suggested that this protein interferes with successful remyelination and functional tissue restoration. Moreover, in patients with progressive MS the ENV protein was detected at lesion rims and being expressed by myeloid cells. ENV protein was then shown to activate primary microglial cells and to confer a myelinated axons-damaging phenotype, therefore providing evidence that microglia mediated neurodegeneration is fostered by this pathological entity. Unpublished data using a transgenic mouse model mimicking the expression of the human specific HERV-W ENV protein confirm these previous observations. Importantly, subsequent clinical trials using an anti-ENV neutralizing antibody, termed Temelimab, revealed decreased atrophy rates. Moreover, stabilized magnetization transfer ratio (MTR) signals were observed in treated participants compared to declining signal changes in control groups. Hence, an impact on neurodegeneration and repair activities by this human specific entity could be confirmed additionally suggesting a strong therapeutic potential of Temelimab.

Key words: Multiple sclerosis, endogenous retrovirus, myelin repair, oligodendroglia, neurodegeneration, microglia

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Update on deep brain stimulation for Dystonia

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Deep brain stimulation (DBS) is an effective and established surgical treatment for several movement disorders, namely Parkinson's disease, tremor and dystonia. Although some clinical trials have confirmed the DBS efficacy in the short and long-term in people with dystonia, several major issues remain to be addressed. First, DBS outcome differs to a great extent in dystonia. This might be related to dystonia etiology, phenotype, genetic contribution. However, parameters of stimulation, stimulation target and anatomical and functional brain connectivity might play an important role. Here, we will review the current knowledge, the gaps and the impact on clinical practice.

The borderland between neurodegeneration and neuroimmunology

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Classically, neurodegeneration and autoimmunity were thought to be two distinct and unrelated mechanisms in neurological disease. In the last years, however, there is increasing evidence for both an inflammatory component in neurodegenerative disease, and neurodegeneration following inflammation in autoimmune disease. Recently, the identification of IgLON5-autoantibodies in patients with a tauopathy has definitely shaken the foundations of the dichotomy between neurodegeneration and neuroimmunology. In this lecture, we will review the broadening clinical spectrum of anti-IgLON5 disease and its red flags, as well as the underlying pathophysiology.

Invasive methods in advanced Parkinson's Disease

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Parkinson's disease is a chronic progressive neurodegenerative disease with no cure so far. There is an urgent unmet need for therapies to modify the inevitable decline that occurs especially in advanced phase. While we are waiting for neuroprotection and cure, a lot of clinical investigation and technical solution were made to improve treatment of advanced phase. Advanced stages of Parkinson's disease are accompanied by a broad scale of motor and non-motor complications which negatively impact patients' quality of life. The therapeutic influence of these complications resulting from the neurodegenerative nature of the underlying disease and are additionally caused by long-term use of dopaminergic treatment, represents a serious clinical problem. Recently, the therapeutic strategy has been focused on continuous dopaminergic stimulation to achieve the balanced control of symptoms. With disease progression and drug-induced complications conventional pharmacological procedures often fail to control clinical symptoms. Alternative methods rise to the forefront of therapeutic interest as they play an important role in the treatment of advanced Parkinson's disease. These options include deep brain stimulation (DBS), subcutaneous application of apomorphine or by pen and levodopa/

carbidopa or levodopa/carbidopa/entacapone intestinal gel therapies, brain lesioning with different techniques (radiofrequency thermocoagulation, radiosurgery, magnetic resonance imaging-guided focused ultrasound surgery (MRgFUS). Correct patient selection, consideration of specific non-motor symptoms and potential risks accompanying individual treatment modalities, significantly contribute to the selection of most appropriate procedure. The treatment of PD has made great progress over recent decades and has directly contributed to an improvement in patients' quality of life, especially through the progression of advanced treatment. Some investigations were a great example of the interplay between basic and clinical science, especially deep brain stimulations. Novel technical models and solutions are investigating and developing first on experimental animal models and then on human. The ideas of origin, translational elements and scientific bases and outcomes of invasive treatment methods will be presented in the lecture.

DBS in patients with disorder of consciousness

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OBJECTIVE An effective treatment of patients in a minimally conscious state (MCS) or vegetative state (VS) caused by hypoxic encephalopathy or traumatic brain injury (TBI) is not yet available. Deep brain stimulation (DBS) of the thalamic reticular nuclei has been attempted as a therapeutic procedure mainly in patients with TBI. The purpose of this study was to investigate the therapeutic use of DBS for patients in VS or MCS. **METHODS** Fourteen of 49 patients in VS or MCS qualified for inclusion in this study and underwent DBS. Of these 14 patients, 4 were in MCS and 10 were in VS. The etiology of VS or MCS was TBI in 4 cases and hypoxic encephalopathy due to cardiac arrest in 10. The selection criteria for DBS, evaluating the status of the cerebral cortex and thalamocortical reticular formation, included: neurological evaluation, electrophysiological evaluation, and the results of positron emission tomography (PET) and MRI examinations. The target for DBS was the centromedian-parafascicular (CM-pf) complex. The duration of follow-up ranged from 38 to 60 months. **RESULTS** Two MCS patients regained consciousness and regained their ability to walk, speak fluently, and live independently. One MCS patient reached the level of consciousness, but was still in a wheelchair at the time the article was written. One VS patient (who had suffered a cerebral ischemic lesion) improved to the level of consciousness and currently responds to simple commands. Three VS patients died of respiratory infection, sepsis, or cerebrovascular insult (1 of each). The other 7 patients remained without substantial improvement of consciousness.

CONCLUSIONS Spontaneous recovery from MCS/VS to the level of consciousness with no or minimal need for assistance in everyday life is very rare. Therefore, if a patient in VS or MCS fulfills the selection criteria (presence of somatosensory evoked potentials from upper extremities, motor and brainstem auditory evoked potentials, with cerebral glucose metabolism affected not more than the level of hypometabolism, which is judged using PET), DBS could be a treatment option.

Keywords: BAEP = brainstem auditory evoked potential; DBS = deep brain stimulation; DR = Rappaport Disability Rating Scale; EEG = electroencephalography; MCS = minimally conscious state; VS = vegetative state

Role of MRI in a modern treatment of neurodegenerative diseases

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The increasing prevalence of neurodegenerative diseases has resulted in serious medical and socioeconomic problems. Although the definitive diagnosis of neurodegenerative diseases is pathologically confirmed via autopsy, living patients are diagnosed according to clinically established diagnostic criteria.

Structural imaging is the imaging workhorse of neurodegeneration, most widely used and accessible. It is recommended in diagnostic guidelines, and it forms part of most consensus criteria. Structural MRI provides information about atrophy pattern, assesses vascular burden and excludes brain lesions. There are several grading systems widely used in clinical practice that are well established. Frequency of misdiagnosis of neurodegenerative diseases only based on clinical symptoms increases the need for objective biomarkers. Recent advances in magnetic resonance imaging (MRI) techniques can determine brain pathological changes *in vivo*.

Advanced MRI techniques are of special interest due to their potential to characterize the signature of each neurodegenerative condition and help in diagnostic process and monitoring of disease progression. MRI techniques are different, from visual inspection to more complex manual and automatic volume measurements, diffusion tensor MRI, and functional MRI. Diffusion Tensor Imaging (DTI) and resting state functional MRI sequences can characterize functional connections and disconnections between brain areas in normal and damaged brains *in vivo*, to provide early diagnosis and track disease progression.

Diffusion tensor imaging (DTI) is a widely utilized diffusion MRI technique in clinical and research settings of neurodegenerative diseases, however, it has several limitations. To overcome these limitations, advanced diffusion MRI techniques, such as diffusional kurtosis imaging (DKI), neurite orientation dispersion and density imaging (NODDI) and free water imaging (FWI), have been proposed primarily for research purposes as models for estimating the microstructures of brain tissue without application in clinical practice.

ABSTRACTS - MINI SYMPOSIUM

Genetics and Parkinson's disease progression

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Parkinson's disease is a common extrapyramidal disorder with an onset around 65 years of age. Onset before age 50 is considered as early-onset Parkinson's disease, and ~15% of Parkinson's disease patients are familial. Parkinson's disease is a multifactorial disease, and an estimated 5-10% can be contributed to monogenic causes. The genetic landscape of Parkinson's disease is comprised of rare high penetrance pathogenic variants that cause familial forms of the disease, while genetic risk factor variants drive Parkinson's disease risk in a significant minority of Parkinson's disease cases. Furthermore, high frequency, low penetrance variants, contribute to a small risk of developing sporadic Parkinson's disease.

Mutations in genes such as SNCA, PRKN, LRRK2, PINK1, DJ-1, VPS35, and GBA, are known in the last thirty years to be important risk factors for Parkinson's disease. In addition, common variants with small effect sizes are now recognized to modulate the risk for Parkinson's disease. Patients with known genetic Parkinson's disease have now been followed for more than twenty years, and we see that they may have distinct and different prognoses. New therapeutic possibilities are emerging based on the genetic cause underlying the disease, enabling personalized approaches to treatment. Therefore, future medication may be based on the pathophysiology individualized to the patient's genetic background.

Microbiota and Parkinson's disease progression

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Parkinson's disease (PD) is a neurodegenerative disease with a multifactorial etiopathogenesis. The main pathophysiological mechanism involves the loss of dopaminergic neurons due to α -synuclein accumulation. Accumulating evidence have identified microbiota as a potential factor in the earliest, prodromal phases of the disease. Thus far, research has shown a significant difference between microbiota composition in PD patients as opposed to healthy controls. Furthermore, the relative abundance of certain microbiota has been correlated with motor and non-motor symptom severity, with varied findings between different bacterial taxa. Besides microbiome composition, metabolic side-products of microbiota with potential effects on Parkinson's disease have also been identified, with short-chain fatty acids (SCFA) being the most prominent ones. Various therapeutic approaches targeting gut microbiota have also been explored, such as antibiotics, prebiotics, probiotics, specific diets as well as fecal

microbiota transplantation (FMT) and enema. At the Clinic for Neurology of the Clinical Hospital Center Rijeka, we are currently conducting a longitudinal study with *de-novo* patients and are looking to add to the current knowledge of both symptom and abundance correlation, and the effects of therapy on the composition of microbiota. Further research into the field could offer a better and more individualized approach to Parkinson's disease treatment.

Electroencephalography (EEG) and Parkinson's disease progression

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Parkinson's disease (PD) is the second most common neurodegenerative disorder which affects more than 8.5 million people worldwide. The neuropathology findings include the loss of dopaminergic neurons in the substantia nigra, the presence of Lewy bodies and Lewy neurites caused by α -synuclein aggregation, and neuroinflammation in the brain. Diagnosis and long-term monitoring of Parkinson's disease (PD) is mainly assessed with clinical rating scales which can be imprecise and subjective. An objective and non invasive measure of disease like EEG could be very valuable in everyday clinical practice.

Nigro-striatal circuits are known to regulate thalamo-cortical activity, which underlies the behavior of cortical electrical rhythms. Therefore electroencephalography (EEG) has been proposed to distinguish PD subtypes, track disease progression, and allow evaluation of treatment responses to symptomatic pharmacological treatment as well as deep brain stimulation (DBS). Quantitative EEG (qEEG) used in studies applies sophisticated mathematical and statistical analysis to measured brainwaves through EEG and compares them to age and gender controlled, analyzing the electrical activity of the brain to derive quantitative patterns that may correspond to diagnostic information and/or motor and cognitive deficits. Movement abnormalities and cognitive decline are related to changes in EEG spectrum and event-related potentials (ERPs) during peculiar paradigms and/or combined motor tasks. Typically abnormalities in β and δ frequency bands are the main manifestation of dyskinesia and cognitive decline in PD, but there have been noted changes in specific EEG characterizations. In conclusion, number of studies findings strongly suggest a link between EEG changes and motor decline. These findings indicate that EEG assessment may be a useful biomarker for objective monitoring of disease progression and neurophysiological effect of different treatment approaches in PD's.

Transcranial sonography and Parkinson's disease progression

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The use of transcranial sonography (TCS) to assess substantia nigra has become an important tool for diagnosis of various movement disorders. Transcranial sonography has been widely accepted for the assessment of Parkinson's disease since the first description of substantia nigra hyperechogenicity in Parkinson's disease patients in 1995. It has also been used for other movement disorders. Anatomical structure is described as hyperechogenic if measured area of the echogenic signal within a defined brain area

is larger in the patient than in the general population or if the visually rated intensity of the ultrasound signal is increased compared with the surrounding brain tissue. The signal is not associated with disease severity and the size of increased echogenicity of the SN does not change with disease progression. The ultrasound marker could be used for the early diagnosis of Parkinson's disease. Because of the stability of this structural marker, it cannot be used to monitor the progression of Parkinson's disease. Complementary information for disease progression still needs to be obtained from clinical assessment and from functional neuroimaging techniques that visualize the integrity of presynaptic neurons. TCS has both advantages and limitations. Advantages of TCS include non-invasive approach, low cost, wide availability, real-time imaging, repeatability and bedside availability. The main limitations are dependence on the experience of the examiner, insufficient temporal bone window and quality of the ultrasonud system. TCS is a useful supplementary method for movement disorders.

YOUNG RESEARCHER FORUM ABSTRACTS

Functional movement disorders after DBS implantation – a case report

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Functional (psychogenic) movement disorders are movement disorders with an underlying psychological cause. Mostly, they present as involuntary movements, sometimes hardly discernable from disorders with an organic background. Another challenge for diagnosis and treatment is an actual movement disorder underlying them, such as Parkinson's disease, making it even harder to make out whether the symptoms are a part of the disease itself or a psychological problem.

We present 2 cases of Parkinson disease patients treated with deep brain stimulation who we suspected developed functional movement disorders. Both patients had a background of anxiety. Moreover, one of the patients also had problems with levodopa addiction. In both cases, we combined suggestion with slight alterations to stimulation parameters ultimately leading to the reduction of symptoms and lower UPDRS III scores upon discharge.

We conclude that the approach to functional movement disorders superimposed on organically caused movement disorders should combine both neurological and psychological methods for best results.

Compared effects of magnetic resonance guided focused ultrasound and deep brain stimulation – a case report

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Magnetic resonance guided ultrasound (MRgFUS) is a non-invasive technique recently proposed as a potential alternative to deep brain stimulation (DBS) in movement disorders such as essential tremor and Parkinson's disease. As far as we know, there have been no reports of DBS following unsuccessful MRgFUS. We present the case of a Parkinson's disease patient, a dentist by profession, who first decided on MRgFUS because of diminishing results of pharmacotherapy. Initially, he showed some improvement, but only for a short period of time. Three years later, he was implanted with DBS, after which his symptoms were vastly improved, eventually allowing him to return to work.

We conclude that, MRgFUS, even though showing promising results, still requires additional research to determine its long-term effects while DBS has already been proven and tested as a valid method for the treatment of Parkinson's disease both short-term and long-term.

A Croatian regional center experience on the effect of the COVID-19 pandemic on Parkinson's disease

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Introduction: The COVID-19 pandemic began in Wuhan, China, in December 2019 and has since drastically altered many facets of human life. People belonging to risk groups were forced to limit their social life and reduce the number of contacts. Any change in behavior that greatly alters a person's life cause psychological stress, which can worsen motor and non-motor symptoms of Parkinson's disease. The main aim of this study was to assess the effect of social isolation due to the COVID-19 pandemic on physical and mental health in Croatian Parkinson's disease patients.

Methods: This cross-sectional study enrolled 170 patients who had at least one control examination at the Clinic of Neurology of the Clinical Hospital Center Rijeka in 2020 and were Croatian citizens. The final sample included 87 successfully interviewed patients.

Results: This study had several important findings. First, most of our patients reported worsening of motor symptoms since the beginning of the pandemic, especially those living alone. Second, the majority of our patients had anxiety problems. Higher HAM-A scores were observed in patients who lived alone, were less educated, had a longer disease duration, and avoided checkups. Third, compared with motor and anxiety symptoms, fewer patients had problems with depression, mostly those with longer disease duration. Fourth, many patients reported worsening of non-motor symptoms, which was especially expressed in those who lived alone, were less educated, had a longer disease duration, and had higher Charlson comorbidity index scores.

Conclusion: Patients who live alone during the pandemic need more care from their families. Greater care should also be given to patients who avoid check-ups and they should be offered counseling due to increased anxiety prevalence. More attention should be directed to non-motor symptoms as they positively correlate with motor symptoms

Acute transverse myelitis after BNT162b2 immunization – a case report

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Transverse myelitis is a rare immune-mediated disease with spinal cord injury, resulting in motor, sensory and autonomic function loss. Vaccine-related acute transverse myelitis is observed in several clinical trials as the rapid application of vaccines continues. We present a case of acute transverse myelitis after vaccination against COVID-19 with the BNT162b2 vaccine. The patient initially presented with paresthesia on the right foot, later spreading to the right thigh, progressive muscle weakness, especially when climbing stairs. The patient was hospitalized because of subacute asymmetric paraparesis with pyramidal characteristics and ataxia. Extensive demyelinating lesions were seen in the cervical and thoracic segments of the spinal cord as well as the medulla oblongata using magnetic resonance imaging. The electropherogram of the spinal fluid detected elevated gamma globulins, suggesting

immunological activity in the CNS. Treatment with high doses of pulse corticosteroids (methylprednisolone 4.5g/7days) resulted in significant improvement in sensory and motor function. The clinical symptomatology, neuroradiological findings and detected globulins suggest acute transverse myelitis (or possibly an initial presentation of multiple sclerosis). Because more than three vertebral segments are affected, it is necessary to rule out neuromyelitis optica spectrum disorders. Additional analyses are required including serological, for ruling out vasculitis (ANA, ANCA, AFA, anti-Jo, anti-Hu, SS-A, SS-B) and aquaporin-4 for neuromyelitis optica. Further study is needed for proper diagnosis and management of post-vaccination neurological complications.

Lingual Dyskinesia in a Patient with Trigeminal Nerve Injury – A Case Report

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Introduction/Objectives: Isolated lingual dyskinesia is a form of orofacial dyskinesia, characterized with involuntary movements of the tongue and can greatly diminish quality of one's life. Etiologically, it is most commonly associated with long-term use of antipsychotic medication, but may also occur in brain damage, neurodegenerative diseases such as neuroacanthocytosis or Wilson's disease and metabolic disorders. The pathophysiology of this disease remains unclear and treatment options limited. The mandibular nerve is the terminal branch of the trigeminal nerve. Its motor component innervates the muscles of mastication, and the sensory component carries information from the lower third of the face (lower lip, the jaw, preauricular area, the temporal area and the meninges of the anterior and middle cranial fossa).

Materials/Methods: A 73-year-old female presented with a 3-month history of burning sensation of the tongue and mouth accompanied by involuntary movements of the tongue. There was no history of psychiatric disease, neuroleptic use or trauma, and her chronic illnesses (type two diabetes mellitus, hypertension, dyslipidemia and paroxysmal atrial fibrillation) were successfully managed with medication.

Results: Routine laboratory test results were within reference range, and the neurological and general examination was normal. The thyroid function tests were unremarkable, B12 and folate levels within normal range. Thus, further imaging diagnostic methods were required to determine the cause of lingual dyskinesia. Cerebral MRI revealed mild diffuse atrophy and microangiopathic white matter changes, with no other abnormalities. SPECT detected mild cortical hypoperfusion. Dopamine transporter scan showed normal function of nigrostriatal dopaminergic system, whilst evoked potentials showed unilateral lesion of mandibular branch of the trigeminal nerve.

Conclusions: Focal tongue dyskinesia is rarely described, poorly understood, and determining its cause may be challenging. Based on the diagnostic procedures and evoked potential test results, our patient's symptoms could be attributed to the lesion of mandibular nerve. Therefore, we emphasize the need for additional research of the relationship between involvement of the afferent fibers of the trigeminal nerve in involuntary movements and their contribution to a complex pathophysiology of this disease.

Niemann-Pick disease type C- progressive neurological deterioration in a 10-year-old girl

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Introduction: Niemann-Pick disease type C (NPC) is a rare autosomal recessive lysosomal disorder associated with an accumulation of sphingomyelin in reticuloendothelial and parenchymal tissues caused by mutations of NPC1 or NPC2 gene. Clinical features include a wide spectrum of visceral and neurological signs and symptoms with onset age ranging from the perinatal period to late. The 'classical' presentation is also referred to as the late-infantile or juvenile form seen in children younger than 5 years of age to adolescence, where learning disabilities, behavioral problems and progressive motor impairment become evident. The aim of this report is to suggest that the early phases of NPC can be overlooked or misdiagnosed due to the heterogeneous and non-specific nature of the symptoms. Case report: A n 8-year-old female patient was referred to the pediatric neurologist for multidisciplinary examination of the autism spectrum disorder. The mother indicated normal gross motor milestones: sitting without support at 7 months, walking independently at 15 months and first words at 16 months. Around the age of 3, the patient underwent an upper lip suturing repair, without sedation. Few months after, her mother noticed a drastic change in behavior and a regression in all aspects of development, which she related to the traumatic event. During neurological examination the patient was anxious, had poor verbal and non-verbal comprehension and facial dysmorphism. At 10-year-old she developed signs of progressive neurological deterioration with frequent epileptic seizures. Brain MRI showed areas of hypo/dysmyelination in the periventricular occipitoparietal region. The patient was referred for genetic testing where 2 pathological mutations of NPC1 gene were confirmed. Conclusion: NPC should be suspected in pediatric patients presenting with developmental delay or regression. Diagnostic algorithm includes genetic testing, skin biopsy and bone marrow examination. NPC can be treated with miglustat, a drug which is associated significantly with reduction of mortality.

COVID-19 induced worsening of Parkinson's disease symptoms in two patients treated with invasive therapies

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COVID-19 complicates the clinical course of Parkinson's disease (PD). Patients with advanced PD treated with invasive therapies are especially vulnerable. Herein, post-COVID-19 syndrome manifests as an acute or subacute worsening of previously stable pre-existing disease symptoms. We present two patients admitted to the Clinic of Neurology Rijeka due to the exacerbation of PD symptoms following COVID-19 infection. The first is a 66-year-old woman diagnosed with PD in 2013 and treated with deep brain stimulation of the subthalamic nucleus in 2017. She was stable for years, but her

symptoms worsened after overcoming COVID-19. She developed fatigue, gait impairment, and leg paresthesia, while increases in rigor and tremor were found during the neurologic examination. Treatment included changes in stimulation parameters and physical therapy. The second patient is a 70-year-old woman diagnosed with PD in 2008. Invasive therapy with levodopa/carbidopa pump was initiated in 2014. Her post COVID-19 symptoms included lack of appetite, increased rigor, apathy, insomnia, and freezing of gait. She took extra levodopa doses, which ultimately caused dyskinesia. The neurological examination revealed discrete hypomimia, mild intentional tremor and bradykinesia, bent gait with apparent dyskinesia. The psychiatric evaluation confirmed a mild depressive episode. Laboratory blood analysis showed abnormalities in kidney function, vitamin D levels and a mild anemia, that could contribute to the worsening. The dosage of levodopa/carbidopa was adjusted. Both patients were discharged with an improved clinical status. The presented cases suggest that PD patients undergoing invasive therapies may experience worsening of motor and non-motor symptoms due to the post-acute COVID-19 syndrome.

Our experience in detection of short tandem repeat expansions from exome sequencing data in patients with neurodegenerative disorders

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Neurodegenerative disorders affect a wide variety of cognitive and bodily functions including memory and learning, language skills, behavior and movement. Progressive damage to the nervous system has several different etiologies including genetic causes, which can be heritable monogenic disorders or risk factors and modifiers of disorders with common idiopathic etiology. Monogenic neurodegenerative disorders are genetically heterogenous and can be caused by a wide variety of genetic variant types including difficult to detect short tandem repeat (STR) expansions.

We selected 555 patients referred for diagnostics at our institution between 2013 and 2022 for neurodegenerative and neuromuscular disorders not associated with STR expansions in which no clinically relevant variants were found using the standard exome analysis approach. We performed bioinformatic STR profiling using Expansion Hunter and report on the clinically relevant results.

Using Expansion Hunter software, we were able to detect 9 STR expansions compatible with the clinical presentation in the patient. We discovered expansion in the pathogenic range in HTT in one patient, DMPK in two patients and ATXN8OS in six patients. All variants were confirmed using triplet repeat primed PCR.

Our study shows that STR profiling improved the diagnostic yield in patients with suspected neurodegenerative disorders. Additionally, bioinformatic STR characterization from exome and genome sequencing data is reliable with all discovered variants being confirmed using an independent method.

A case report of a novel GNB1 mutation and the response to deep brain stimulation

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Introduction: Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions, leading to abnormal involuntary movements or postures. Although many forms of dystonia are still classified as idiopathic, two principal etiologies are identified: inherited genetic alterations and acquired specific causes. The most common genetic causes of dystonia are TOR1A, THAP1, GCH1, and KMT2B mutations, but only a handful of cases have been reported with GNB1 mutation. Case report: We present a 27-year-old woman with a history of difficulty walking, abnormal neck posture and head jerks since childhood. She was diagnosed with dystonia at the age of 14. The symptoms became more severe over time, affecting her entire body and interfering with the majority of her everyday activities. She underwent deep brain stimulation (DBS) of the globus pallidus internus (GPi) at the age of 22 after failing to respond to several oral medications. DBS helped with neck rigidity and head posture, but difficulty walking and involuntary shaking of both hands were still present. Genetic testing performed at the age of 27 showed a heterogeneous, probably pathogenic variant c.352G>C in the GNB1 gene that led to the replacement of aspartate with histidine at the 118th position in the amino acid sequence. This variant isn't described in the single nucleotide polymorphism database nor in the genome aggregation database. Conclusion: In this case report we describe a novel c.352G>C variant in the GNB1 gene. To the best of our knowledge, we present the second case of a GNB1-dystonia treated with GPi-DBS. Therefore, we recommend considering GNB1 mutations in the differential diagnostics of childhood-onset dystonia and that DBS therapy should be considered in these patients.

Genetic evaluation of dystonia

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Background: Dystonia is a clinically and genetically heterogeneous movement disorder, characterized by sustained or intermittent muscle contractions that cause abnormal postures. Dystonia occurs in isolation, in combination with other neurological symptoms (combined) or in association with other systemic signs (complex). The current diagnostic approach proposed by the expert group of the The European Reference Network for Rare Neurological Diseases (ERN-RND) focuses on syndromic evaluation and classification based on two axes, clinical features and aetiology. The aim of this study was to evaluate the common and genetically specific tests used to assess patients with dystonia who are referred to the Clinical Institute of Genomic Medicine in Ljubljana for further investigation. Methods: A retrospective cohort study

of patients presenting with dystonia, referred to the Clinical Institute of Genomic Medicine, UMC Ljubljana, Slovenia. Results: Between 2008 and 2022, 145 patients with dystonia were referred to our institution. Most of them were women (57 %) and there was a slight predominance of onset in childhood or adolescence (51 %). The distribution of dystonia was most commonly generalized (42 %), followed by focal and segmental forms. Isolated and combined or complex clinical features were present in 43 % of cases. Additional neurological features most commonly included ataxia, pyramidal signs, mioclonus and parkinsonism. Brain MRI was available in 53 % of patients. Investigation for acquired forms most commonly included blood tests for Wilson's disease, metabolic tests (thyroid hormones, vitamin E, B12 and folic acid), serological (paraneoplastic, anti-neuronal, systemic autoimmune antibodies) and microbiological tests. Next-generation sequencing was performed in 120 patients and identified pathogenic or likely pathogenic variants in 12.5 % of these patients, involving 14 different monogenic causes in the genes UFM1, NPC1, SPEN, THAP1, ADNP, MPZ, PANK2, TSEN54, TBK1, CHD8, FGF14, SLC2A1, YY1, GNB1 and a likely pathogenic interstitial duplication 15q11.2-q13.1. Molecular-genetic tests for a three base-pairs deletion in TOR1A (c.907_909delGAG, DYT1) were performed in 26 % of patients. Conclusions: According to the current recommendations for the diagnostic evaluation of dystonia, we identified a pathogenic or likely pathogenic variant in 12.5 % of patients, which is comparable to the diagnostic yield reported by other authors.

Functional neurological disorder in Parkinson's disease treated with deep brain stimulation: a case report

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Introduction: Deep brain stimulation (DBS) has been established as a highly-effective therapy for advanced Parkinson's disease (PD). Functional neurological disorder (FND) is part of a wide spectrum of functional disorders. The predominant feature is a loss or alteration in physical functioning that suggests a physical disorder, but ultimately is without a clear substrate. FND is usually a direct expression of a psychological conflict or need, and presents with a wide range of symptoms or false worsening that can affect even advanced PD patients treated with DBS.

Case report: We present a 54-year-old patient with a history of right-sided tremor and bradykinesia. The diagnosis of Parkinson's disease was given at the age of 46, with levodopa therapy shortly after. Progression of the disease was relatively fast and DBS therapy was indicated at the age of 53. The neurological exam revealed hypophonia, right-hand tremor, bradykinesia and mild gait impairment despite therapy. Bilateral subthalamic nucleus (STN) DBS was performed the same year. Initial response to DBS was tremendously positive, with the patient regaining significant work capability. However, the patient reported worsening that often coincided with work or household related obligations. Several months after implantation, the patient was admitted to the Clinic of Neurology Rijeka due to claimed worsening. During the

hospitalization, the levels of stimulation and levodopa doses were adjusted several times, which reduced bradykinesia and tremor. However, a discrepancy between subjective symptoms and objective findings was seen. Interestingly, the patient reported improvements even in the sham DBS parameter changes.

Conclusion: This case report signifies the importance of suspecting a functional disorder in patients treated with DBS, as reported worsening of symptoms can occur with no clear substrate.

A COVID-19-Related Worsening of Dystonia in Two Patients Treated with Deep Brain Stimulation

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Introduction: Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions, causing abnormal involuntary movements or postures. The most common genetic causes of dystonia are TOR1A, THAP1, GCH1, and KMT2B mutations, but only a handful of cases have been reported with a GNB1 mutation. The neurotropic SARS-CoV-2 virus, that causes Coronavirus Disease 2019 (COVID-19), presents a great challenge to our whole society. To the best of our knowledge, there are no published cases of dystonia worsening after SARS-CoV-2 infections in deep brain stimulation (DBS) treated patients.

Case report: We present two patients with generalized dystonia treated with GPI-DBS. They were admitted to the Clinic of Neurology Rijeka due to worsening of symptoms following a COVID-19 infection and consequently, the requirement for DBS parameters adjustment. The first patient is a 27-year-old female with GNB1 dystonia (c.352G>C, Asp118His), and the second patient is an 8-year-old male with DYT28 dystonia (KMT2B gene, c.5572dupC; p.Arg1858Profs*114). Both patients experienced a mild form of COVID-19, with headaches being the most noticeable symptom. Worsening of dystonia occurred two weeks following the acute COVID-19. The symptoms became considerably worse when the stimulation parameters were increased, but rapid improvement happened when the stimulation parameters were reduced.

Conclusion: Both of our patients had headache as one of the symptoms during COVID-19 infection. Headaches could possibly indicate CNS invasion, causing an inflammatory response that leads to neuronal hyperexcitability. We hypothesize that the possible changes in neuronal excitability caused the ineffectiveness of previous DBS stimulation parameters, which could be why lowering the stimulations helped and why the effect was not permanent.

Successful three-year outcome of Deep Brain Stimulation in Gaucher Disease type 1 associated Parkinson's disease: A case report

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Introduction: Gaucher's disease type 1 (GD1) is an autosomal recessive disease caused by mutations in the glucocerebrosidase (GBA) gene. Parkinson's disease (PD) with GBA mutations is characterised by early fluctuations, motor complications and cognitive decline, thus being specific and challenging to treat. The clinical standard of care for treating advanced PD is deep brain stimulation. To the best of our knowledge, only two cases of deep brain stimulation (DBS) treatment of PD in GD1 have been reported so far, both patients in their 50's and with successful and sustained results.

Case report: We present a case of a 43-year-old man who was diagnosed with GD1 in 2010, with following causative compound heterozygote mutations found: c.882T>G, p.H294Q, c.1226A>G, p.N409S, c.1342G>C, p.D448H. He had a rapid progression during five years to an advanced state of PD, with early fluctuations and dyskinesias. We proposed early DBS therapy to the patient due to severe motor fluctuations and side-effects, with prior neuropsychological testing. Patient's symptoms and quality of life improved significantly with STN-DBS due to greatly improved functioning with no dependence on help.

Conclusion: DBS should be considered in early on in GD1-PD patients who have a positive, but fluctuant, response to levodopa therapy, as the potential benefits on the quality of life are significant. However, it is essential to give special care to proper cognitive screening before the procedure and continue to monitor cognitive performance regularly.

Introduction to evidence-based clinical practice guidelines

Katina Aleksovska

European Academy of Neurology, Guideline Production Group

Clinical practice guidelines (CPGs) are systematically developed statements which main aim is to standardize and improve the everyday clinical practice. To achieve this, the guideline developers make systematic reviews and meta-analyses on particular topics of interests, and use standardized approaches in the judgment of the available evidence. To further increase the relevance of the recommendations, CPGs are developed by teams of experts in the particular fields, and patient representatives of the medical conditions that the CPGs are aimed at. Using this approach, CPGs have the ability to disseminate the best available evidence to every practicing physician.

However, often the evidence used in the CPGs is not sufficient to provide straightforward answers, the final decisions should be supported by the judgment of the practicing physician and the affected patients. The basic knowledge on the methodology behind CPG production and the formulation of the recommendations could help to base these judgements on the evidence disclosed in the CPGs and to improve the patient important outcomes even when the decisions are hard to make due to the uncertainty of the evidence.

In this lecture, I will provide a short overview of the methodology used in CPG development by using examples of the recent CPGs of the European Academy of Neurology. Furthermore, I will explain the terminology behind particular levels of recommendations that should provide insights into the decisions to what extent and in which situations particular recommendations can be applied into practice.

Microglia-dependent neurodegeneration is fueled by the human endogenous retrovirus W envelope protein

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Axonal degeneration is central to clinical disability and disease progression in multiple sclerosis (MS). Myeloid cells such as brain resident microglia and blood-borne monocytes are thought to be critically involved in this degenerative process. However, the exact underlying mechanisms have still not been clarified. We have previously demonstrated that human endogenous retrovirus type W (HERV-W) negatively affects oligodendroglial precursor cell (OPC) differentiation and remyelination via its envelope protein (ENV) (formerly MS-associated retrovirus [MSRV]-ENV). In a current study, we investigated whether HERV-W ENV also plays a role in axonal injury in MS. We found that in MS lesions, HERV-W ENV is present in myeloid cells associated with axons. Focusing on progressive disease stages, we could then demonstrate using an ex vivo myelination model that HERV-W ENV induces a degenerative phenotype in microglial cells, driving them toward a close spatial association with myelinated axons. Moreover, in HERV-W ENV-stimulated microglia were found to structurally damage myelinated axons. Taken together, our data suggest that HERV-W ENV-mediated microglial polarization contributes to neurodegeneration in MS (published in Kremer, Gruchot et al., PNAS (2019); <https://doi.org/10.1073/pnas.1901283116>). For functional validation in vivo, we currently analyse neuronal- and glial cell responses, remyelination and neurodegeneration in a novel HERV-W ENV expressing transgenic mouse model, the current findings of which will be presented here.

Thus, this analysis provides a neurobiological rationale for a recently completed clinical study in MS patients showing that antibody mediated neutralization of HERV-W ENV exerts neuroprotective effects.

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