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

Symposium

3rd RIJEKA FORUM ON NEURODEGENERATIVE DISEASES DIAGNOSIS AND TREATMENT IN EARLY STAGE OF DISEASE

Endorsed by Associations

Parkinson i mi, Neurodeg and Ean

Rijeka, October 17-18, 2019
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

Daniel Rukavina, president
Vladimira Vuletić, Nenad Bogdanović, Vida Demarin

Organizing Committee

Vladimira Vuletić, president
Vjera Fererri Matković, Zoran Tomić, Valentino Rački, Srđan Novak

Registration: 8,30 – 9,30 am

Free admission. Participants who want a certificate from the Croatian Medical Chamber need to register.
Refreshments during breaks and lunch are with no charge.
Parking is free and provided in the building of Student Centar Rijeka (Radmile Matejčić 5)

Information

Željana Mikovčić, Department of Biomedical Sciences in Rijeka
Radmile Matejčić 2, Rijeka
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PROGRAM
OPENING
(9,30 – 10,00)

Introduction

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

Vladimira Vuletić, M.D., PhD, Assistant Professor, Medical Faculty, University of Rijeka, Rijeka; President of the Organizing Committee

Welcome addresses

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

Davor Štimac, M.D., PhD., Professor, Head of the Clinical Hospital Center Rijeka, Rijeka

Tomislav Rukavina, M.D., PhD., Professor, Dean of the Medical Faculty, University of Rijeka, Rijeka

Vida Demarin, M.D., PhD., Professor, Secretary of the Department of Medical Sciences, Croatian Academy of Sciences and Arts, Zagreb

10,00 – 12,30 h

I. GENETIC, CEREBROSPINAL FLUID AND PATHOLOGY

Chairmen: Vida Demarin and Vladimira Vuletić

John Hardy, PhD, Professor, UCL Institute of Neurology, London, UK
Genomics of neurodegeneration

Borut Peterlin, M.D., PhD, University Clinical Center Ljubljana, Ljubljana, Slovenia
Personalized approach to patients with Parkinson's disease based on their genetic background

Coffee break: 11,00 – 11,30

Kaj Blennow, M.D., PhD, Professor, Gothenburg University, Gothenburg and Mölndal Campus, Mölndal, Sweden
Current status for cerebrospinal fluid and blood biomarkers for Alzheimer's disease

Tamas Revesz, M.D, Professor Emeritus, University College London, London, UK
What can we learn from the neuropathological study of preclinical and early neurodegenerative diseases?

Lunch with a panel of speakers: 12,30 – 13,30

13,30 – 16,00 h

II. DIAGNOSTICS AND PREVENTION

Chairmen: Tamas Revesz and Alessandro Padovani

Vida Demarin, M.D., PhD, Professor, International Institute for Brain Health, Zagreb
Lifestyle factors in prevention of cognitive decline

Paolo Manganotti, M.D., PhD, Professor, University of Trieste, Trieste, Italy
Clinical Neurophysiology measures in Neurodegeneratve disorders

Alessandro Padovani, M.D., PhD, Professor, University of Brescia, Institute of Neurology, Brescia, Italy
Cholinergic and dopaminergic alterations in early Alzheimer's disease: emerging findings from TMS and DATSCAN

Maja Trošt, M.D., PhD, Assistant Professor, University Hospital Centre Ljubljana, Ljubljana, Slovenia
PET FDG as a biomarker of an early stage of neurodegenerative diseases

Leja Dolenc Grošelj, M.D., PhD, Associate Professor, University Clinical Center Ljubljana, Ljubljana, Slovenia
Sleep as an early marker for neurodegenerative disorders

2nd day – October 18th, 2019

9,00 – 11,00 h

III. CLINICAL ASPECTS AND TREATMENTS

Chairmen: Nenad Bogdanović and Sten Fredrikson

Sten Fredrikson, M.D., PhD, Professor, Karolinska Institute, Stockholm, Sweden
Early detection of multiple sclerosis - when does the disease really start?

Tomislav Babić, M.D., PhD, Professor, Neuroscience Franchise Worldwide Clinical Trials, London, UK
Overcoming challanges in clinical trials of multiple system atrophy and dementia with Lewy bodies

Nenad Bogdanović, M.D., PhD, Professor, Karolinska Institute, Stockholm, Sweden
Dementia in Alzheimer and Lewy Body: so different yet so similar

Fran Borovečki, M.D., PhD, Professor, University Hospital Centre Zagreb, Zagreb, Croatia
Early diagnosis of Fronto - Temporal Dementia (FTD)

Coffee break: 11,00 – 11,15

11,15 – 14,30 h

Chairmen: Fran Borovečki and Darko Chudy

Nataša Klepac,M.D., PhD, Assistant Professor, University Hospital Centre Zagreb, Zagreb, Croatia
Early diagnosis of Corticobasal Syndrome (CBS) and Progressive Supranuclear Palsy (PSP)

Darko Chudy, M.D., PhD, Professor, University Hospital Centre Dubrava, Zagreb, Croatia
Early Deep Brain Stimulation (DBS) in movement disorders

Vladimira Vuletić, M.D., PhD, Assistant Professor, Clinical Hospital Center Rijeka, Rijeka
Biomarkers of early Parkinson's disease

Lunch with a panel of speakers: 12,45 – 13,30

Leopold M.G. Curfs, M.D., PhD, Rett Expertise Centre Netherlands, Maastricht, Netherlands
Rett syndrome as a rare disease within an European context

Eric Smeets, M.D., PhD, Rett Expertise Centre Netherlands, Maastricht, Netherlands
Rett syndrome and developmental regression

14,30 – 15,00 h

II. GENERAL DISCUSSION AND CLOSING

Chairman: Vladmira Vuletić

Genomics of neurodegeneration

John Hardy
UCL Institute of Neurology, London WC1 3BG, United Kingdom

In the last 10 years our understanding of neurodegenerative diseases has proceeded rapidly as we have become able to move from identifying only Mendelian causes of disease to identifying risk loci for "sporadic" disease. In my talk I will have two broad aims. First to review this progress and second to propose a unifying view of how the sporadic and Mendelian forms of these disease are related. I shall propose that in general late onset sporadic diseases reflect failures in protein clearance. In Alzheimer's disease the majority of loci are microglial. In Parkinson's disease many are lysosomal and in the tauopathies they are involved in proteostasis including the ubiquitin proteasome. I will discuss how these findings are consistent with a simple view that the primary deposited proteins, Ab, synuclein and tau are close to their crystalisation points and either over production or poor clearance can lead to disease.

Personalized approach to patients with Parkinson's disease based on their genetic background

Borut Peterlin[1,2]
[1]Clinical Institute for Genomic Medicine, Ljubljana, Slovenia
[2]University Clinical Center Ljubljana, Ljubljana, Slovenia

Parkinson disease is etiologically and clinically heterogeneous disorder. Heterogeneity is reflected with challenges in early recognition and diagnosis, prediction of prognosis and selection of therapies.
Monogenic forms of the disease have provided pathogenetic insights and have important implications for diagnosis, prevention, and prognosis. On the other hand, polygenic risk scores have the potential to predict risk for disease as well as prognosis and therapeutic efficiency.
Lastly, genetic variation in genes involved in the metabolism of drugs might predict the efficacy of treatment and side effects.
In this paper, we will provide an overview of the current evidence for the use of genetic information in a personalized approach to Parkinson disease.

Current status for cerebrospinal fluid and blood biomarkers for Alzheimer's disease

Kaj Blennow[1,2]
[1]Institute of Neuroscience and Physiology,
[2]University of Gothenburg, Mölndal Campus, Sweden

Alzheimer's disease (AD) has a variable clinical presentation that is difficult to diagnose on pure clinical grounds, especially in the early mild cognitive impairment (MCI) phase. Therefore, biomarkers reflecting the core pathologies, amyloid deposition (A) with plaques, tau pathology (T) with tangles, and neurodegeneration (N) are crucial for clinical diagnostics. Accurate diagnosis will be especially important given the promise of disease-modifying drugs, and also for clinical trials, to assure inclusion of patients that do have Alzheimer-type pathology.

Today, the AD cerebrospinal fluid (CSF) biomarker toolbox includes assays covers the core AD pathology, including b-amyloid (Ab) aggregation (Ab42 or Ab42/40 ratio), tau phosphorylation (P-tau), and neurodegeneration (total tau, T-tau) have very consistently been found to have high diagnostic accuracy, also in the MCI disease stage.
Recent additions to the AD CSF biomarker toolbox are the neurodegeneration biomarker neurofilament light (NFL) and the synaptic biomarker neurogranin. While CSF NFL tracks the intensity of neurodegeneration not only in AD but also in several other brain disorders, increased CSF neurogranin is seemingly specific for AD, and predicts future rate of cognitive decline.
Using novel techniques, brain biomarkers can also be measured in blood samples. Several studies using either immunoassay (Simoa) or immunoprecipitation - mass spectrometry (IP-MS) techniques suggest that low Ab42 (or Ab42/40) ratio in plasma correlate with amyloid deposition evaluated by PET scans. Plasma NFL levels correlate well with CSF levels, and may a tool to monitor neurodegeneration. Recent studies also show very promising results on P-tau181 in blood samples, with a very clear increase, tight correlations with CSF levels, and high concordance with tau PET. Blood biomarkers may have value as screening tools in the future, e.g. in the primary care setting.

What can we learn from the neuropathological study of preclinical and early neurodegenerative diseases?

Tamas Revesz
Queen Square Brain Bank for Neurological Disorders,
UCL Institute of Neurology, University College London,
Queen Square, London, WC1N 3BG,
United Kingdom

Understanding patterns of neuropathological progression in neurodegenerative diseases is of paramount importance with implications on our understanding how such diseases evolve clinically. As a consequence, such knowledge can contribute to establishing appropriate biomarkers allowing early clinical diagnosis.
In the past over two decades, it has become clear that from the earliest disease stages neuropathological progression takes place in an anatomically determined, stereotypic manner. As a general rule, at least in sporadic diseases, neuropathology is thought to start in well-defined, circumscribed anatomical areas of the central nervous system from where it progresses in a predictable manner to additional cerebral regions via pre-existing neural networks. Although the mechanisms which are able to trigger the initial pathological changes remain enigmatic, sufficient data have emerged to indicate that disease progression is closely associated with misfolding, aggregation and, importantly cell-to-cell transmission of disease-associated proteins.
The significant body of data that is relevant for understanding disease progression has essentially emerged by studying large cohorts of preclinical cases with early pathological changes, together with cases with intermediate level of clinical presentation and neuropathological changes and also end-stage cases with fully developed clinical presentation and neuropathology. The best studied examples include Alzheimer's disease and Parkinson's disease. In the former both the amyloid-β and tau (neurofibrillary) pathologies while in the second the Lewy (α-synuclein) pathology have been shown to progress in anatomically determined, stereotypic manner.

In this presentation, patterns of progression of a number of neurodegenerative diseases will be discussed, including Alzheimer's disease, Parkinson's disease, corticobasal degeneration and progressive supranuclear palsy. The significance of studying preclinical cases and cases with early pathological changes will be emphasised.

Lifestyle factors in prevention of cognitive decline

Vida Demarin
International Institute for Brain Health

Greater population life expectancy is one explanation for increased incidence of cognitive decline and dementia. A large number of people with cognitive impairment and dementia is becoming one of the most important medical and social problems worldwide, a kind of a modern epidemic, what is leading to a number of researsh in this particular field.
As there is still no cure for dementia, the focus is on prevention, and acting now on dementia prevention, intervention, and care will vastly improve living for individuals with dementia and their families, and also, potentially decrease its number, and in doing so, will transform the future for society.
Dementia is the greatest global challenge for health and social care in the 21st century: around 50 million people worldwide have dementia and this number is predicted to triple by 2050. *The Lancet* Commission on dementia aimed to review the best available evidence and produce recommendations on how to best manage, or even prevent, the dementia epidemic.
Dementia is not an inevitable consequence of ageing and the Commission identifies nine potentially modifiable health and lifestyle factors from different phases of life that, if eliminated, might prevent up to 35% of dementia, being: low education in early life, hypertension, obesity and hearing loss in midlife and diabetes, depression, physical inactivity, smoking and social isolation later in life.
Studies are going on investigating the role and importance of potential changes of different lifestyle factors to prevent cognitive decline.
Epidemiological and prospective studies have shown that regular physical activity improves cognitive functions, fights depression and protects from neurodegenerative diseases. Extensive research is going on to prove biological mechanisms that underlie such beneficial effects. Multi-domain interventions could improve or maintain cognitive functions in at-risk elderly people (FINGER study, 2015.). Higher values of BDNF, as well as greater grey matter volume, measured by MRI, were found with higher aerobic activity, pointing out that it might be neuroprotective.
Results of PREDIMED and other studies showed the value of the Mediterranean diet, not only for prevention of stroke, but for prevention of cognitive decline as well.
Interventions to reduce obesity, stopping smoking, maintaining a vital social environment, positive attitude and many more, as well as building up resilience and brain reserve and activation of neuroplasticity, could decrease cognitive decline.
Having in mind, more than a century old sentence of Santiago Ramon y Cajal that „Every man can, if he so desires, become a sculptor of his own brain" , the time has obviously come to teach the people how to work on that.

Key words: cognitive decline, dementia, lifestyle factors, prevention neuroplasticity

Clinical Neurophysiology measures in Neurodegeneratve disorders

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

Mild (MCI) and Subjective Cognitive Impairment (SCI) are conditions at risk of developing Alzheimer's disease (AD). Differential between normal aging at early stages can be really challenging; available biomarkers need to be combined and can be quite invasive and expensive. Many studies have investigated the EEG alterations in MCI and SCI compared to controls, analyzing if a cognitive task could highlight early AD hallmarks. In EEG studies during cognitive task, ŚÁ-band power reduction was found predominantly in frontal regions in SCI and CS, diffused to all regions in MCI; moreover, decreased EEG complexity was found in SCI compared to controls. The ŚÁ -band power attenuation restricted to frontal regions in SCI during a free recall task (involving frontal areas), suggests that MCI patients compensate for encoding deficit by activating different brain networks to perform the same task. Furthermore, ha been reported that EEG complexity reduction - that has been found already in SCI - could be a possible early hallmark of AD.Many studies draws attention on the importance of high level analysis approach in EEG analysis and the potential role of cognitive task in highlighting EEG alterations at very early stages of cognitive impairment; EEG could therefore have a practical impact on dementia diagnosis. In recent years, several evidences supported the concept that loss of synaptic density could be an early event and precede neuronal degeneration, suggesting that the impairment of synaptic transmission should play a key role in the pathogenesis of different forms of dementia, including AD, frontotemporal dementia and Lewy body dementia. Despite this emerging background it has not been possible to quantify synaptic functioning (or dysfunction) directly in vivo in AD patients. Cholinergic dysfunction is a key abnormality in Alzheimer disease (AD) that can be detected in vivo with transcranial magnetic stimulation (TMS) protocols. Although TMS has clearly demonstrated analytical validity, its clinical utility is still debated. In the present presentation we evaluated the incremental diagnostic value of TMS measures in addition to the routine clinical diagnostic assessment in patients evaluated for cognitive impairment as compared with validated biomarkers of amyloidosis. Assessment in patients with dementia has a significant effect on diagnosis and diagnostic confidence that is comparable to well-established amyloidosis Transcranial magnetic stimulation (TMS) has been recently introduced as a novel approach able to identify the early signatures of synaptic dysfunction characterizing the different forms of AD. We will describe the novel emerging neurophysiological signatures of AD and how this information may be used as biomarkers for differential diagnosis, disease progression and response to therapy.
Finally, we also describe the novel therapeutic approaches based on the clinical use.

Cholinergic and dopaminergic alterations in early AD: emerging findings from TMS and DATSCAN

Alessandro Padovani, Andrea Pilotto, Alberto Benussi, Valentina Cantoni, Sara Nocivelli, Barbara Paghera, Daniela Perani, Barbara Borroni[1,2]

[1]University of Brescia

[2]University San Raffaele of Milano

Background: Pathological reports suggest that, in addition to choloinergic system, dopaminergic and serotonergic pathways are early involved in Alzheimer's disease (AD). By using TMS and 123I-FP-CIT SPECT imaging, there is the possibility to investigate in vivo different neurotransmitter systems. In fact, paired-pulse TMS has been shown to be a method for evaluate glutamatergic, gabaergic and cholinergic pathways whereas 123I-FP-CIT SPECT imaging allows the evaluation of both dopamine transporter (DAT) and serotonin transporter (SERT) in several brain regions.

Aim: to evaluate cholinergic and extrastriatal dopaminergic and serotonergic pathways in AD patients.

Methods:. Alzheimer's disease patients were included in a multicenter study and underwent a standardized neurological examination, structural imaging and CSF/amyloid imaging in order to reach a biomarker diagnosis of AD (i.e. A+T+N+ classification). A paired-pulse TMS multi-paradigm approach assessing multiple intracortical circuits, as short interval intracortical inhibition-facilitation and short latency afferent inhibition, was administered to controls (n= 70) and patients fulfilling criteria for AD (n=108). A subgroup of AD (=52) patients performed 123I-FP-CIT SPECT imaging and the bindings of extrastriatal regions of interests were calculated from spatially normalized images. The occipital-adjusted specific to non-displaceable binding (SBR) in the different regions was compared among AD and controls adjusting for the effect of age, sex, disease duration and serotonergic/dopaminergic treatment.

Results: We observed a significant impairment in short latency afferent inhibition (SAI) in AD whereas short interval intracortical inhibition-facilitation (SICI/ICF) was normal, irrespective of disease severity. According to ROC curve analysis, the SICI-ICF/SAI index was the best differentiating parameters differentiating prodromal AD from prodromal DLB with a specificity of 96,1% and a sensitivity of 94.2%. Alzheimer' s disease patients showed lower 123I-FP-CIT SPECT SBR in cingulate (p=0.001) and temporal lobe (p=0.007) as well as in insula (p=0.01) and thalamus (p=0.025) compared to controls. When dividing AD according to severity, MCI (n=17) showed significantly lower cingulate SBR compared to controls (p=0.017) and significantly higher SBR in insula, thalamus and temporal lobe (p=0.01) compared to AD with dementia (n=35).

Conclusions: Alzheimer's disease present with early cortical and subcortical diffuse neurotransmitter impairment affecting either cholinergic circuits or extrastriatal dopaminergic or serotonoergic pathways. These alterations appeared to be present already at MCI stage. Longitudinal studies will be necessary in order to evaluate the clinical value of these pathways for possible different pattern of progression and response to treatment in AD patients.

FDG PET as a biomarker of an early stage of neurodegenerative brain diseases

Maja Trošt
University Medical Center Ljubljana, Slovenia

The common neurodegenerative brain diseases have a long and slowly progressive course. Although the diagnosis of dementia and parkinsonisms can be made when the typical clinical presentation develops, pathophysiological processes begin many years earlier. The concept of a presymptomatic or preclinical disease stages is becoming widely accepted in search for the effective causative treatments for neurodegenerative diseases. One of the possible explanations for this unmet need in neurodegenerative brain diseases is that the treatment trials were so far mostly conducted in patients in whom clinical picture was already developed and the neurodegenerative process in brain too pronounced and widespread. The focus of scientist's' attention has therefore shifted towards earliest phase of diseases, its detection and course. It is now already possible to identify the neurodegenerative diseases at their "silent" preclinical stages even before the occurrence of the first clinical symptoms. Various imaging and fluid biomarkers are being developed for the detection of preclinical neurodegenerative brain disease stages. Metabolic brain imaging with ^{18}F-fluorodeoxyglucose and positron emission tomography (FDG PET) is one of them as it can detect the metabolic brain abnormalities caused by the earliest stages of neuronal dysfunction and neurodegeneration. Besides early disease detection, FDG PET brain imaging can be helpful also for differential diagnosis and for monitoring the disease progression.

Early detection of multiple sclerosis - when does the disease really start?

Sten Fredrikson[1,2]
[1]Karolinska Institutet, Stockholm, Sweden
[2]Karolinska University Hospital, Stockholm, Sweden

Multiple sclerosis (MS) is a chronic inflammatory and degenerative disease of the central nervous system. The age at clinical onset and diagnosis of MS is usually between 20 to 40 years of age, but symptoms may occur both at earlier and later phases of life. MS is a potentially disabling disease with a great impact on the life of the patient and the patient´s family. The symptoms of MS are highly variable between different individuals, including sensory and motor disturbances, problems with vision, bladder, coordination, speech and also "invisible symptoms" with complaints of pain, depression, fatigue and cognitive impairment. The diagnostic criteria for MS have been changed and adapted in 2001, 2005, 2011 and 2017 with the aim of enabling as early and accurate diagnosis as possible. The improved techniques of magnetic resonance imaging (MRI) have recently revealed frequent and progressive cortical lesions in MS, a disease previously considered to be an inflammatory disease of the white matter. The findings of progressive brain volume loss, including both grey and white matter, in MS have increased the interest in a evaluating the degenerative component of the disease. During recent years, the possibility of an important primary degenerative component in the disease pathogenesis has been discussed. Previously it has usually been considered that the degenerative aspects are secondary to the inflammation, but several factors indicate a progression from the earliest phases of the disease, eg detection of early brain volume loss at imaging. The use of biomarkers, like neurofilament light, also

support the concept of early axonal damage. Whether MS is a disease with two stages including initial attacks of inflammation leading to relapses, followed by a switch to a degenerative progressive stage or whether MS is a relentless progressive disease from onset is at present a hot research topic. It is of great scientific interest to further evaluate the degenerative early aspects to refine the therapeutic tools that still are directed towards the inflammatory component of the disease. The more widespread use of MRI of the brain in persons with different non-MS complaints, eg headache, head trauma etc, has lead to accidental detection of typical radiological findings compatible with MS in these persons. The concept has been established during the latest decade as radiological isolated syndrome (RIS) denoting MS typical radiological findings in persons without clinical symptoms and signs indicative of MS. A follow-up of these persons have shown that 2/3 will develop new MR-findings and 1/3 will develop clinical manifest MS within a five year follow-up period. Thus, when we talk about "early MS" the disease processes may already have been active for years in advance of the first clinical manifestation of the disease. The best management of these pre-clinical forms of MS is being discussed and the first clinical trials of disease-modifying MS therapies in persons with RIS have been initiated, although RIS is still not included in the diagnostic criteria of MS.

Sleep as an early marker for neurodegenerative disorders

Leja Dolenc Grošelj
University Clinical Center Ljubljana, Ljubljana, Slovenia

Sleep disturbance is a common symptom in patients with various neurodegenerative diseases, including Alzheimer's (AD), Parkinson's disease (PD) and dementia with Lewy Bodies (DLB). Sleep changes can manifest in the early stages of these diseases.
Impaired sleep in patients with AD has been attributed to AD pathology that affects brain regions regulating the sleep-wake or circadian rhythm. AD patients often experience difficulty falling asleep, repeated nocturnal arousals, early arousals in the morning, and excessive sleepiness during daytime. One or more sleep disorders, including insomnia, circadian rhythm sleep–wake disorders, sleep-related breathing disorders (SRBD), and sleep-related movement disorders, underlie these symptoms. The alterations in the diurnal rhythm of activity and sleep due to circadian rhythm dysregulation are also present in patients with preclinical AD and symptomatic AD.
Contrary to the conventional understanding that impaired sleep in patients with AD is a consequence of AD-related pathology, multiple recent epidemiological studies have suggested that sleep disturbance could be a risk factor for cognitive decline and AD. These studies have led to the idea of a bidirectional relationship between AD and impaired sleep.
Rapid eye movement (REM) sleep behavior disorder (RBD) is a REM sleep parasomnia characterized by dream enacting behaviors allowed by the loss of physiological atonia during REM sleep. This disorder is recognized as a prodromal stage of neurodegenerative disease, in particular Parkinson's Disease (PD) and Dementia with Lewy Bodies (DLB) and is considered to be a promising biomarker predicting conversion to manifested synucleinopathy.
As RBD is an early feature of DLB and often precedes the onset of other core features, a clinical history of RBD enables us to improve the low diagnostic sensitivity of DLB at

the early stage of disease progression. Moreover, RBD is an accurate predictor of DLB in terms of the differential diagnosis of dementia based on clinical and pathological findings.
Furthermore, elucidating the link between impaired sleep and the dynamics of proteins that accumulate in each disease (such as α-synuclein in PD and DLB as well as Aβ and tau in AD) could lead to the development of a novel disease-modifying therapy for neurodegenerative diseases.

Literature:

1. Minakawa EN, Wada K, Nagai Y. Sleep Disturbance as a Potential Modifiable Risk Factor for Alzheimer's Disease. Int J Mol Sci. 2019, 13; 20(4).
2. Nepozitek J et al. Simultaneous tonic and phasic REM sleep without atonia best predicts early pheno conversion to neurodegenerative disease in idiopathic REM sleep behavior disorder. Sleep. 2019 Jun 13. pii: zsz132. doi: 10.1093/sleep/zsz132. [Epub ahead of print]
3. Fujishiro H. Revised 2017 Clinical Diagnostic Criteria for Dementia with Lewy Bodies: Inclusion of REM Sleep Behavior Disorder and Indicative Biomarkers. Brain Nerve. 2018;70(8):869-877. doi: 10.11477/mf.1416201096. Review.

Dementia in Alzheimer and Lewy Body: so different yet so similar

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

The two neuropathological hallmarks of Alzheimer disease (AD) are the extracellular Aβ plaques and the intracellular neurofibrillary tangles, of which the latter is composed of hyperphosphorylated tau protein. Lewy bodies are intraneuronal cytoplasmic inclusions comprising aggregates of α-synuclein and are readily detected by immunohistochemistry using anti–α-synuclein antibodies. In up to 50% of cases of sporadic late-onset AD, comorbid Lewy bodies are found. Lewy bodies are frequent in the setting of moderate-to-severe levels of AD neuropathologic change. Neuroanatomical studies indicate that Lewy body accumulation follows a stereotypic pattern starting in the brainstem nuclei/olfactory regions and progressing to limbic areas and, in the most advanced stages, to the neocortex. In contrast to this stereotypical pattern, Lewy bodies in AD may also be found concentrated in the amygdala without significant involvement of the brainstem or neocortical regions a distribution that has been called AD with amygdala Lewy bodies. These cases with both Lewy body and AD pathology are variously termed Lewy body variant of AD, AD with dementia with Lewy bodies (DLB), or AD with Lewy bodies. Many patients with DLB also have overlapping Alzheimer's disease, which is why some patients are misdiagnosed. While the two forms of dementia have similarities, there are some important distinctions. Alzheimer's affects the brain's ability to store new information in the form of memories, while DLB targets a different set of cognitive functions – specifically problem solving and reasoning. The distinctive patterns of neuropsychological dysfunction observed in these dementias probably represent a different distribution of pathological changes. The neuropathological substrate of AD affects predominantly the medial temporal cortex and the neo-

cortical association areas, which explains the predominant dysfunction of episodic memory function. On the other hand, the neuropathological basis of DLB includes neuronal loss and the presence of Lewy bodies in the subcortical nucleus and in the frontal and parietal lobes, which explains the predominantly attentional, executive, and visuospatial dysfunctions.

Symptoms and **memory** can vary significantly in DLB, such that on one day your grandmother might not recognize you and the next day, she can recall the names of each of her grandchildren. In AD cognition can vary somewhat but typically the person's ability to think and use his memory gradually declines over time. In AD there is not usually a big variance from one day to the next. **Visual hallucinations**, where people see things that aren't actually there, are quite common in occur early in DLB but only after about four years in Alzheimer's disease. These hallucinations typically occur earlier in the progression of DLB. Hallucinations do occur in AD but are generally not as prevalent as in DLB. They also tend to occur in the later stages of AD. People with DLB sometimes experience **REM sleep behavior disorder (RBD)**, a dysfunction where they physically act out the situations in their dreams. It has been suggested that RBD can be one of the earlier predictors of DLB. RBD is not typically present in AD, although other types of sleep disturbances may occur. Often, one of the early symptoms of **parkinsonism** in DLB is difficulty walking, a decrease in balance and frequent falling is also common early in DLB. In AD physical deterioration usually does not occur until the disease has significantly progressed, unless the individual has other diseases or illnesses. Patients with DLB display a *flat affect*, where their faces show very little emotion. This is another symptom that may present early in the disease and overlaps with Parkinson's. In AD facial **expressions** often decrease as the disease progresses, this often does not develop until the middle to later stages of AD.

Individuals with DLB have a very high risk of serious **side effects if antipsychotic medications** that are given to them. Up to 50% of patients with DLB who are treated with any antipsychotic medication may experience severe neuroleptic sensitivity, such as worsening cognition, heavy sedation, increased or possibly irreversible parkinsonism, or symptoms resembling neuroleptic malignant syndrome (NMS), which can be fatal. (NMS causes severe fever, muscle rigidity and breakdown that can lead to kidney failure). In AD, patient who takes an antipsychotic medication has a small risk of developing neuroleptic malignant syndrome. **Disease progression** may differ between DLB and AD. The median survival time for those with DLB is 78 years old, and survival after onset of dementia is 7.3 years. The median survival time for patients with AD is 84.6 years, and the survival rate after the beginning of symptoms is 8.4 years. It has been suggested that the difference in the disease progression between DLB and AD can partially be explained by the increase in falls, and therefore injuries and hospitalizations, in those with DLB. **Gender-wise** men have a higher chance of developing DLB than women do, while women have a higher chance of developing AD. DLB in comparison with AD is a multi-system disease and typically requires a comprehensive **treatment** approach, meaning a team of physicians from different specialties, who collaborate to provide optimum treatment of each symptom without worsening other DLB symptoms. It is important to remember that some people with DLB are extremely sensitive or may react negatively to certain medications used to treat Alzheimer's or Parkinson's in addition to certain OTC medications. Medications called cholinesterase inhibitors are considered the standard treatment for cognitive symptoms in DLB and

AD. These medications were developed to treat Alzheimer's disease. However, people with DLB may be even more responsive to these types of medications than those with AD. Movement symptoms may be treated with a Parkinson's levodopa medication but in much less doses, but if the symptoms are mild, it may be best to not treat them in order to avoid potential medication side-effects. If visual hallucinations are disruptive or upsetting, it is suggested a newer antipsychotic medication especially those that spare cholinergic system. Of note, the dementia medications with AChE inhibitors have also been shown to be effective in treating hallucinations and other psychiatric symptoms of DLB. RBD can be quite responsive to treatment, so a medication like melatonin and/or clonazepam can be recommended. Severe sensitivity to neuroleptics is common in DLB. While traditional antipsychotic medications (e.g. haloperidol) should be avoided risperidone and quetiapine can be preferred. Some TH-3 antagonists have been suggested to treat visual hallucinations. In general, as a rule of thumb a treatment should be very conservative, using the lowest doses as possible under careful observation for side effects. Non-medical treatments are widely suggested such as *physical therapy* options include cardiovascular, strengthening, and flexibility exercises, as well as gait training for both dementias. *Speech therapy* may be helpful for low voice volume and poor enunciation. Speech therapy may also improve muscular strength and swallowing difficulties especially in DLB. *Occupational therapy* may help maintain skills and promote function, while *individual and family psychotherapy* and *support groups* may be helpful for caregivers and persons with both dementias to identify practical solutions to day-to-day frustrations, and to obtain emotional support from others.

Early diagnosis of Progressive Supranuclear Palsy and Corticobasal Syndrome

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Corticobasal syndrome (CBS) is a clinical diagnosis that comprises a group of rare neurodegenerative diseases manifesting in movement disorder and cognitive impairment. It usually presents with akinetic-rigid parkinsonism, dystonic and myoclonic movements, associated with cortical symptoms such as ideomotor apraxia, alien limb phenomena, aphasia or sensory neglect. Previously was thought that CBS is manifestation of corticobasal degeneration but recently published studies have demonstrated that CBS is phenotypic manifestation of diverse pathologies, including Alzheimer's disease, 4-repeat tauopathies, frontotemporal lobar degeneration, dementia with Lewy bodies, and Creutzfeldt-Jakob disease. It was concluded that CBS is highly heterogeneous clinical condition, the etiology of which can thus far only be ascertained with post mortem pathological exam. Classic corticobasal degeneration pathology is found in only 25% to 56% of CBS cases. Progressive Supranuclear Palsy (PSP) once simply considered a common cause of atypical parkinsonism is now recognized as a spectrum of motor and behavioral syndromes associated with a specific four repeat (4R) tau neuropathology at autopsy. New research criteria that recognize early forms of PSP (International Parkinson's and Movement Disorder Society (MDS) Criteria for the Diagnosis of PSP) have recently been published. They define early, "suggestive" forms of PSP and diagnosis of the full spectrum of clinical phenotypes. According to the new concept of neurodegeneration it is assumed that PSP starts with a presymptomatic phase in

which neuropathological abnormalities begin to accumulate but clinical features are absent, develops to an suggestive of PSP (soPSP) phase in which individuals develop mild or isolated symptoms, but do not meet the full research criteria for PSP, and culminates with a fully symptomatic stage. Presymptomatic PSP occurs in individuals who are asymptomatic but possibly destined to develop a full-blown PSP. Currently, the presymptomatic phase can only be identified post mortem by evidence of histological changes typical of PSP pathology in individuals who are considered clinically normal. There are several variants of PSP with Richardson syndrome (PSP-RS) as most often encountered. Two thirds of the neuropathologically-defined cases of PSP in brain banks presented in the first two years with PSP-RS and moreover most PSP syndromes progress to develop some or all of the typical clinical features of PSP-RS. Other PSP syndromes are named according to their predominant clinical features and include PSP predominant parkinsonism (PSP-P), pure akinesia with gait freezing (PSP-PGF), corticobasal syndrome (PSP-CBS), primary progressive apraxia of speech or non-fluent variant primary progressive aphasia (PSP with predominant speech/language disorder or PSP-SL), behavioral variant frontotemporal dementia (PSP with predominant frontal presentation or PSP-F) and PSP with predominant cerebellar ataxia (PSP-C). When fully developed, the PSP-RS clinical syndrome is distinctive and usually easily differentiated from other parkinsonian disorders. However, in early or variant cases, increasing evidence suggests that biomarkers may help to improve diagnostic accuracy. Recognition of individuals in the early symptomatic PSP stage of disease is crucially important since early recognition could potentially allow neuroprotective treatment to be initiated early enough to stabilize individuals before the onset of significant disability. A variety of neuroimaging and biochemical biomarkers for PSP have been described to aid in differential diagnosis and evaluation of novel therapeutics offering hope for patients and their families for the possibility of effective PSP therapies.

Early Deep Brain Stimulation for movement disorders

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Movement disorders include neurological conditions characterized by disorders in speed, fluency, quality and ease of movement. Although surgical treatments for movement disorders were applied to human patients since 1930s, the most important evolution for the surgical treatment of movement disorders came with the introduction of frame-based surgery. The first researches that used the subthalamic nucleus as the Deep Brain Stimulation (DBS) targeting point showed the advantage of DBS over conventional medicaments therapy. Since then, DBS has become an established option for treating patients with various movement disorders whose pharmacological therapy is no longer effective in suppressing symptoms. In the long run, significant improvements in motor function, tremor, dyskinesia and rigidity were observed for five years and more after DBS implantation. In the last 20 years, our group has successfully treated more than 150 patients with movement disorders, namely Parkinson's disease and dystonia. The majority of symptoms in patients were significantly reduced, and they were enabled to continue an active life and functioning in society.

Biomarkers of early Parkinson's disease

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Parkinson's disease (PD) is the second most common chronic age-related, progressive neurodegenerative disorders. The hallmark symptoms of PD include motor features (bradykinesia, postural disturbances, rigidity or tremor or both) and nonmotor features (hyposmia, sleep disorders, autonomic, neuropsychiatric and sensory symptoms). The diagnosis of PD depends mostly on clinical motor findings (cardinal symptoms) which appear when 60-80% of the substantia nigra (SN) dopamine neurons are lost. PD is, therefore, often diagnosed clinically when disease progression is already advanced. But, a long latency between the first damage to dopaminergic cells and the onset of clinical symptoms is known and this is a time where we can do something to stop the disease. Therefore, it is very important to find reliable biomarkers that can distinguish PD in an early phase, to let interventions at the onset of disease and to monitor the progress of therapeutic interventions that may slow or stop the course of the disease. Identifying a successful biomarker depends inevitably on fully understanding the pathophysiology underlying the disease. In PD, despite remarkable advances in our insight into the responsible mechanisms, the etiology remains unknown. The key neuropathology in PD is Lewy body deposition (abnormal aggregates of a misfolded protein called α-synuclein) and consequently neuronal dysfunction, involving many other brain areas and neurotransmitter systems. In their early research, Brack et al. proposed a staging scheme based on rostro-caudal pathological progression and it was suggested that in the earliest stages, PD damage is confined to non-dopaminergic structures in the lower brainstem, the olfactory bulb or perhaps the peripheral autonomic nervous system, accounting for the early appearance of non-motor symptoms To date, only symptomatic treatments exists for PD.

Clinical diagnosis of PD is challenging (especially in the early stages of the disease), due to high misdiagnosis rate (10-30 % for early stages), as symptoms show fluctuating clinical syndrome over time. In addition, there are numerous overlapping symptoms with other morbidities (e.g. such as essential tremor, multiple system atrophy, and progressive supranuclear palsy). Research in recent years, prompted by epidemiological data on risk factors and prodromal biomarkers, has proposed diagnostic criteria based upon the likelihood of prodromal disease (with 80% certainty). This has been recently reviewed and also includes changes in the gut microbiome in patients who have REM sleep behavior disorder or Parkinson disease, REM sleep behavior disorder and later genetic and autonomic cohorts, olfactory loss, substantia nigra hyperechogenicity, neurogenic and symptomatic orthostatic hypotension, and age related penetrance. Diabetes, global cognitive deficit, physical inactivity, and low plasma urate levels in men enter the criteria as new markers. PD biomarkers can be subdivided into four main types: clinical, imaging, biochemical and genetic. It is also important to know potential risk factors like environmental toxins, drugs, pesticides, brain micro trauma, focal cerebrovascular damage, and genomic defects. Innovative approaches with combination of prodromal symptoms and imaging or biochemical biomarkers to identify individuals at high risk of developing motor-PD are well-known. One of them is taken by the PREDICT-PD study, which combines the presence of mood symptoms

and/or RBD with results from smell testing, genotyping, and keyboard-tapping tasks to divide individuals into high-risk, middle-risk, and low-risk groups. In the era of precise and personalize medicine, the goal of these and other multimodal screening tools is to identify a population at significant risk of PD both to improve counseling for individual patients as well as to identify a potential population for clinical trials of disease-modifying agents and the best drugs (pharmacogenetics) at a stage where intervention is likely to be most effective. Thus, early recognition and diagnosis is crucial to the future of PD management. The development of appropriate biomarkers that facilitate the early diagnosis, detecting disease progression and the discovery of new treatments for PD are crucial for better clinical management of PD patients. In this presentation will be explored the recent advances in PD biomarker research for disease diagnosis and disease surveillance from a variety of clinical,biochemical, genetic and neuroimaging perspectives.

Rett syndrome as a rare disease within an European context

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Rett syndrome is a rare neurological disease of genetic origin, in most cases attributable from a loss of function mutation in the gene encoding Methyl-CpG-binding Protein 2 (*MECP2*). In this lecture we focus on Rett syndrome in the European context of rare diseases, rare disease policy and rare disease initiatives. The applied and more fundamental research conducted by the Rett Expertise Centre Netherlands –Governor Kremers Centre will be cited within this broader European context. Treatment of Rett syndrome is a lifelong challenge for clinicians and researchers all over the world. The level and type of services and support offered to individuals with Rett syndrome and their families varies between the European countries. The role of national Rett parent associations and Rett Expertise Centres within the European Union for maximizing approaches towards treatment and long-term management will be discussed.

Rett syndrome and developmental regression

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Developmental regression is a hallmark of Rett syndrome (RTT), a neurological disease whose ongoing pathology is still being unravelled. Symptoms include loss of acquired skills, especially in relation to communicative and motor performance. Clinical developmental profiles, non-specific early in life, become more specific later in life. In order to support clinical diagnosis, a staging system has been developed as a framework that delineates the evolving symptoms. This includes stages of early-onset stagnation, rapid developmental regression, a pseudo-stationary stage and late motor deterioration. The most recent revision of the clinical criteria for diagnosis of typical and atypical RTT (Neul et al., 2010) allows for a broader interpretation of regression and partial recovery than was previously acknowledged. Clinicians should be aware of these criteria, for counselling of families as they seek to understand the stages their child will encoun-

ter and for the application of management strategies that may help to ameliorate or compensate for loss of skills at the different stages across the lifespan. RTT is caused by a loss of function mutation in MECP2, an important regulator of gene expression. We do not yet fully understand the biological pathways underlying the outward presentations of the syndrome (Ehrhart et al., 2019). The multi-functionality of MECP2 suggests there are many downstream pathways that are interesting for understanding the pathophysiology of RTT, and allowing a search for drug targets. Further research in these areas should be conducted alongside clinical management that is symptomatic and supportive. For clinicians, it is important to be aware of the natural history of RTT. It is also important to be aware that, as more detailed analyses of early and ongoing aspects of RTT are conducted, our definition of the syndrome and of the benefits to be gained from therapeutic interventions is changing. Most of our knowledge to date comes from a relatively small body of research involving a relatively small number of individuals. Studies such as those conducted by Einspieler&Marschik (2019), and Sigafoos et al. (2019) are helping to refine our understanding of the phenotypic complexity of the syndrome and the potential to respond to treatments and therapies. What is not yet clear is which interventions are best applied at which stages. Research in this area is lacking. Early intervention and comprehensive lifelong individualized management can have a significant impact on the health, quality of life and longevity of affected individuals who are experiencing regression. In the future, as more interventions are documented and delivered, our descriptions and expectations of the later stages may well also be revised.

Overcoming challanges in clinical trials of multiple system atrophy and dementia with Lewy bodies

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Multiple-system atrophy (MSA) is a rare progressive, neurodegenerative disease characterised by autonomic failure in addition to various features of parkinsonism, cerebellar ataxia, and pyramidal dysfunction. The key neuropathological issue is α-synuclein, aggregates which make glial cytoplasmic inclusions (GCI). It is characterised by severe neuron loss supratentorially in the substantia nigra and posterior putamen; infratentorially in the pons, cerebellum and inferior olives; and spinally in the intermediolateral cell columns. Nonetheless, the pathogenic mechanisms underlying MSA remain unknown, making it difficult to develop effective treatment.
Dementia with Lewy bodies (DLB) is another neurodegenerative disorder associated with α-synuclein aggregation in neurons, characterised by Parkinsonism and cognitive impairment but may also manifest multiple symptoms of dysautonomia, rapid eye movement (REM) sleep behaviour disorders, hallucinations, and cognitive fluctuations. Although well described for several decades, DLB remains a diagnostic challenge due to the clinicopathological overlap with other neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease dementia (PDD) and frontotemporal degeneration (FTD). Despite the fact that DLB is the third the most common form of dementia, the number of therapeutic clinical studies is well below the number that could reasonably be expected and appears to be more in line with the number of studies that might be expected in orphan neurologic disorders. The lack of available interventional

studies is not likely due to the lack of drugs whose mode of action address important symptoms in DLB, but rather due to the diagnostic uncertainty of DLB and the lack of valid and reliable unified rating scales.

Early diagnosis of Fronto - Temporal Dementia (FTD)

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Frontotemporal dementia (FTD) represents a heterogeneous group of neurodegenerative disorders characterized by the selective degeneration of the frontal and temporal cortical lobes. FTD is a common type of dementia, particularly among patients younger than 65 years of age. The term FTD encompasses clinical phenotypes that include changes in behavior, language, executive control, and often motor symptoms. The core FTD spectrum disorders include behavioral variant FTD, nonfluent primary progressive aphasia (PPA), and semantic variant PPA. Related FTD disorders include, among others, frontotemporal dementia with motor neuron disease, progressive supranuclear palsy syndrome, and corticobasal syndrome. Genetics represents an important risk factor for development of FTD, and is believed to be an underlying mechanism in almost 40% of the cases. Recent advances in clinical characterization, structural and functional imaging, as well as genetics have enabled a more accurate and timely diagnosis of FTD. It is believed that these advances may lead to a better understanding of the underlying molecular mechanisms of the disease and development of novel therapies.