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 MEDICAL ASSOCIATION – Branch office Rijeka

Symposium

2nd RIJEKA FORUM ON NEURODEGENERATIVE DISEASES

Endorsed by Associations

Parkinson i mi, Neurodeg and Ean

45. obljetnica Sveučilišta u Rijeci

385. godina visokog obrazovanja u Rijeci

17th October 2018.

9,00 am

University Campus Rijeka, University Departments, Lecture hall O-030, Radmile Matejčić 2, Rijeka

Organizers

THE CROATIAN ACADEMY OF SCIENCES AND ARTS
The Department of Biomedical Sciencies in Rijeka

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Scientific Committee

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

Organizing Committee

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

Registration: 8,00 – 9,00 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
Phone: 051 584 826, e-mail: rimed@hazu.hr

PROGRAM
OPENING (9,00 – 09,15)

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

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

Snježana Prijić – Samaržija, PhD., Professor, Rector of the University of Rijeka, Rijeka

9,15 – 12,00 h

I. KEYNOTE LECTURE

Chairmen: Vladimira Vuletić and Daniel Rukavina

John Hardy, PhD, Professor, UCL Institute of Neurology, London, UK
Genomic analysis of neurodegenerative diseases and possible implications on society

II. BASIC ASPECTS OF DEMENTIAS

Chairmen: Vida Demarin and Tamas Revesz

Tamas Revesz, M.D, Professor Emeritus, University College London, London, UK
Pathological aspects of neurodegenerative dementias

Paolo Manganotti, M.D., PhD, Professor, University of Trieste, Trieste, Italy
Neurophysiological methods in neurodegenerative diseases, especially in dementias

Coffee break: 10,50 – 11,10

Tomislav Babić, M.D., PhD, Professor, Neuroscience Franchise Worldwide Clinical Trials, London, UK
Neuropharmacological news and studies in neurodegenerative diseases especially dementias and multiple sclerosis

Vida Demarin, M.D., PhD, Academician, Professor of Neurology, International Institute for Brain Health, Zagreb
Possibilies of dementia prevention

Lunch with a panel of speakers: 12, 00 – 12,45

12,45 – 16,20 h

III. CLINICAL ASPECTS OF DEMENTIAS

Chairmen: Nenad Bogdanović and Tomislav Babić

Nenad Bogdanović, M.D., PhD, Professor, Karolinska Institute, Stockholm, Sweden
Alzheimer's dementia and Alzheimer-like dementias

Alessandro Padovani, M.D., PhD, Professor, University of Brescia, Institute of Neurology, Brescia, Italy
New insights in Fronto-Temporal dementia

Zvezdan Pirtošek, M.D., PhD, Professor, University Hospital Centre Ljubljana, Ljubljana, Slovenia
Demetia in progressive supranuclear palsy and corticobasal syndrome

Vladimira Vuletić, M.D., PhD, Assistant Professor, Clinical Hospital Center Rijeka, Rijeka
Dementia in Lewy body dementia and Parkinson's disease

Coffee break: 14, 25 – 14,40

14,40 – 16,45 h

IV. OTHER ASPECTS OF DEMENTIAS AND COGNITIVE PROBLEMS

Chairmen: Sten Fredrikson and Fran Borovečki

Fran Borovečki, M.D., PhD, Professor, University Hospital Centre Zagreb, Zagreb, Croatia
Prion associated dementia

Sten Fredrikson, M.D., PhD, Professor, Karolinska Institute, Stockholm, Sweden
Multiple sclerosis and cognitive problems

Nataša Klepac, M.D., PhD, Assistant Professor, University Hospital Centre Zagreb, Zagreb, Croatia
Vascular dementia

Maja Trošt, M.D., PhD, Assistant Professor, University Hospital Centre Ljubljana, Ljubljana, Slovenia
PET and SPECT in neurodegenerative diseases, especially dementias

Borut Peterlin, M.D., PhD, University Clinical Center Ljubljana, Ljubljana, Slovenia
Rare genetic variants: patients with dementia and population

16,45 – 17,10 h

V. UPDATES IN RETT SYNDROME

Chairman: Zvezdan Pirtošek

Eric Smeets, M.D., PhD, Rett Expertise Centre Netherlands, Maastricht, Netherlands
Clinical management of Rett Syndrome

17,10 h

VI. GENERAL DISCUSSION AND CLOSING

Chairman: Vladmira Vuletić

ABSTRACTS

Genomic analysis of neurodegenerative diseases and possible implications on society

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

Genomic analysis of late onset neurodegenerative diseases means that for all the late onset neurodegenerative syndromes, we now have identified many genes involved in their pathgenensis: mendelian genes which cause disease, low frequency high risk loci and common low risk variants. Because the richness of these new data, for the first time we are beginning to see that for each syndrome we see features which diseases for each syndrome have in common. The following is not an exhaustive list but the common features include:

- Alzheimer's disease: microglial response to amyloid deposition
- Late onset Parkinson's disease: autophagy
- Early onset Parkinson's disease: mitophagy
- Frontotemporal dementia: autophagy
- FTD/ALS: the unqiutin proteasome system
- Pure ALS: the RNA stress granule response.

Overarching these commonalities is the observation that all of these are damage response pathways. Thus my over-arching hypothesis is that late onset neurodegenerative disease is a failure in damage response and that different diseases involve different primary causes of damage.
Separately, I will summarise the overall poor results from the Alzheimer's trials of anti –amyloid therapies and discuss the possible reasons for their failure and discuss what we need to be doing to treat these diseases.

Pathological aspects of neurodegenerative dementias

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

Central to the pathomechanism of the neurodegenerative dementias to be discussed in this lecture, is that they are characterised by age-dependent misfolding, aggregation and deposition of disease-specific proteins, hence they belong to the so-called protein folding disorders. A proportion of the neurodegenerative dementias have a genetic cause and genetic risk factors have also been identified in several such conditions including Alzheimer's disease and Parkinson's disease.
The pathological processes underlying neurodegenerative disorders often selectively affect anatomically interconnected, functionally related systems and networks giving rise to characteristic clinical presentations in the different forms of dementia. However, as the distribution of the underlying pathological changes determine the clinical presentation, different diseases may result in a similar clinical presentation. Examples include frontotemporal dementia and the corticobasal syndrome, which may be caused by several distinct pathologies. Furthermore, a disease with characteristic neuropathological changes such as corticobasal degeneration may have several distinct clinical presentations. For example, the different clinical manifestations that can be observed in patients with corticobasal degeneration pathology include not only the corticobasal syndrome, but also a progressive supranuclear palsy syndrome, behavioural variant of frontotemporal dementia and non-fluent variant of primary progressive aphasia and patients rarely may present with cerebellar signs.
As pathologically altered proteins, characteristic for each disease or a group of diseases, form extracellular deposits and/or intracellular inclusions in neurons and in some instances, also in glia, such protein aggregates provide a valuable tool in the everyday neuropathological diagnosis. Although the aetiology of most of the neurodegenerative diseases remains elusive, the significant increase in knowledge about genetic background, cellular events and biochemical changes has allowed the introduction of molecular classifications of neurodegenerative diseases, including dementias, which will be followed in this lecture.

Neurophysiological methods in neurodegenerative diseases, especially in dementias

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

The neurological degnerative disorders are defined on the basis of semeiotic and clinical hystory but the diagnosis can be defined by blood, liquor and genetic biomarkers and by neuroimaging . The clinical neurophysiology used in an appropriate way rapresents an important step in diagnosis and in the monitoring the degenerative neurological disases.
EEG can help in definitions of front temporal and Alzheimer disease. EEG is mandatory in detections of seizures and convulsive seizures that can be underestimated. New method sof EEG connectivity are innovative in the diagnosis of neurodegenerative diseases. The EMG is important in the group of degenerative diseases associated to

motor neuron an it plays an important role in the investigation of pelvic floor in parkinsonisms. Evoked potentisl can be used with the long latency cognitive potentials (P300) to define the attention and the short memory detection.. The TMS can investigate not only the motor pathways but also the brain excitabiltiy using different paramters as the motor threshold, the paired pulse and the conditioning paired pulse that can add important information on disease. Brain stimulation with high frequency stimulaton and theta burst stimulation can also play and important role in the treatment of neurodegeneraive diseases.

Neuropharmacological news and studies in neurodegenerative diseases especially dementias and multiple sclerosis

Tomislav Babić
Neuroscience Franchise Worldwide Clinical Trials, London, United Kingdom

Development of new treatment for neurodegenerative disorders like Alzheimer's disease (AD) and other types of dementia is currently the most disappointing field in CNS drug research. In facts after nearly twenty years no new drug has been approved to treat neither cognitive nor behavioural symptoms in subjects with AD. More than 500 clinical studies have been executed involving more than 30.000 participants in AD since 2000 and no one have met clinically significant primary endpoint in their confirmatory trial design. Plenty of explanations have been offered including inappropriate preclinical models, inadequate dose selection during the translational process, lack of sensitive instruments who will capture small, but clinically significant changes, short study durations, occurrence of numerous research sites usually with limited experience in drug research and many others. Apparently, our knowledge on AD's disease biology is still quite limited, whereas the current concept of drug development targeting inter-neuronal amyloid deposition in the brain has not been confirmed, in spite of numerous clinical studies with various molecules. Inability to find new and successful molecule to treat Alzheimer's disease leaded to enhanced research towards primary and secondary prevention of AD. It seems that today's technology of molecular imaging of the brain can visualise presence of amyloid pathology several years prior to clinical onset of AD. Therefore, there are several ongoing large clinical studies in so called pre-clinical AD subjects where new molecules have been tested with idea to postpone the clinical onset of AD. We eagerly expecting encouraging results from these studies.

Opposite to new drug research for AD, the drug development for the treatment of relapsing remitting multiple sclerosis (RRMS) has made fantastic progress since the first disease modifying treatment agent (DMTA) called interferon beta has been approved for the treatment of RRMS in the early nineties of previous century. Since then, plenty of new molecules have been developed, frequently with better and better efficacy profiles. Unfortunately the occurrence of new and more potent molecules for the treatment of RRMS has not been associated with the improvement with their safety profiles. Therefore, among unmet medical needs in the treatment of multiple sclerosis which are including further delaying progression and avoiding disability; re-myelinisation and repair of degenerated neurons; neuroprotection and more effective reduction of active symptoms, reduction of the cost of treatment and prevention and ameliorating of adverse effects of current medication are the most important challenges of further drug development for multiple sclerosis. There are several ongoing confirmatory clinical studies in multiple sclerosis from which we expect additional therapeutic progress and improvement.

Possibility of dementia prevention

Vida Demarin[1,2]
[1]Croatian Academy of Sciences and Art, Zagreb, Croatia
[2]International Institute for Brain Health, Zagreb, Croatia

Greater population life expectancy is one explanation for increased incidence of cognitive impairment 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 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 dementia. Although therapies are currently not available to modify the underlying disease process, the Commission outlines pharmacological and social interventions that are able to help manage the manifestations of dementia.

The risk of Alzheimer's disease (AD), the most common form of dementia, is in a large part modulated by genetics, but prevalence is decreasing in many high-income countries; hence, modifiable risk factors are also at work. Identifying and tackling these factors is an urgent research priority, for which the network is a step in the right direction. Analysis of population-based data found that about a third of AD cases in the USA and Europe were attributable to seven potentially modifiable risk factors: physical inactivity, smoking, midlife hypertension, midlife obesity, diabetes, depression, and low educational attainment. The findings suggested that, by targeting these risk factors with public-health interventions, disease prevalence could be substantially reduced. That about a third of dementia cases might be preventable is now corroborated by findings in *Dementia prevention, intervention, and care* done by already mentioned The Lancet Comission on Demetia. The Commission adds social isolation and midlife hearing loss to the list of relevant epidemiological factors, and comes up with a hypothetical life-course model of their contribution to dementia. The model estimates that 35% of dementia cases could be prevented if these risk factors were eliminated; hence, a key recommendation of the Commission is to "be ambitious about prevention" of dementia, focusing on interventions to build up resilience and brain reserve, to activate neuroplasticity, detect and treat risk factors and to live healthier lifestyles.

Having in mind, 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.

Alzheimer disease and Alzheimer-like dementias

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

Alzheimer's disease (AD) is the main cause of dementia and accounts for 60% of dementia syndromes in people older than 75 years. Memory impairment, especially impairment of episodic memory, is one of the first symptoms of typical AD[1]. Alzheimer-like clinical picture is often assumed to be the underlying cause of dementia in elderly patients. Thus, it is highly important to establish the correct diagnosis and be aware of medical conditions that may by presenting with memory impairment mimicking AD. The correct classification of AD and non-AD is mandatory to study disease mechanisms or new treatment possibilities. The term "memory" generally means the ability to reproduce or remember experienced or learned content. Although there are fewer common syndromic variants of AD, one of its main and early features is an impairment of episodic memory. Episodic memory is an essential cognitive function that supports our ability to form an autobiographical history and helps us to create a concept of the past and the future[2]. The hippocampal network, including the parahippocampal gyrus, hippocampus, and neocortical areas, play a major role in the process of memory consolidation and retrieval[3]. Virtually any neurological, neurodegenerative, toxic, or traumatic damage to brain structures involved in episodic memory generation, especially the hippocampus, may lead to deficits in episodic memory that may resemble or precede AD[4], especially in the absence of other neurological or neuropsychological symptoms or signs indicative of an alternative cause. The diagnostic procedure of memory impairment is firstly based on a comprehensive clinical investigation, that should comprise a detailed medical/medication history, proxy report of the perceived symptoms, neuropsychological testing, and a neurological and psychiatric examination. Additional investigations, such as a magnetic resonance imaging (MRI) scan, 18fluorine-2-deoxy-D-glucose positron emission tomography (18F-FDG-PET), cerebrospinal fluid (CSF) examination, electroencephalography (EEG) and AD biomarkers (β-amyloid42 [Aβ42], ratio Aβ42/Aβ40, total tau protein [t-tau], and phosphorylated tau [p-tau]), may further help to establish the correct diagnosis. A typical clinical picture for AD consists of a slowly progressive memory loss and loss of praxis and speech, absence of medical, neurological, or psychiatric condition that may explain the memory loss, brain imaging that is in line with AD, and biomarkers supporting the diagnosis of AD[5]. Atypical symptoms such as early neurological symptoms, mood disorder, visual hallucinations, or an atypical sudden onset may hint at a diagnosis other than AD. Application of the novel clinical criteria based on biomarkers has shifted a diagnostic procedure "to the left" and has introduced a new concept termed preclinical AD where clinically normal individuals with biomarker evidence of AD pathology were hypothesized to be on the trajectory towards symptomatic AD. The NIA–AA staging framework for preclinical AD is based on biomarker combinations and cognition: stage 1 denotes to amyloidosis without neurodegeneration, stage 2 denotes to amyloidosis plus neurodegeneration and stage 3 denotes to amyloidosis plus neurodegeneration plus subtle cognitive deficit. Use of biomarkers have carried out individuals with mild cognitive impairment who are amyloid-negative but neurodegeneration-positive addressing a conceptually separate clinical entity named suspected non-Alzheimer

disease pathophysiology (SNAP). SNAP clinical progression can mimic AD that makes final diagnose and treatment options uncertain in the clinical centers that are not using biomarkers in the assessment of cognitive impairment. The neurobiological bases non-AD pathologies are common with advancing age in impaired and clinically normal elderly people. These pathologies include cerebrovascular disease, α-synucleinopathy, argyrophilic grain disease, TDP-43 proteinopathy and hippocampal sclerosis[6]. Medial temporal tau pathology without amyloidosis might be a major constituent of SNAP. The term primary age-related tauopathy (PART) has been proposed as a useful practical clinical construct[7] to describe this phenomenon in very old individuals. Furthermore, a clinico-pathological studies[8] demonstrate that aggregated tau distribution in the absence of beta-amyloid is associated with early cognitive impairment (MMT $\geq$ 24), left hippocampus/limbic atrophy, relatively preserved cortex, low frequencies of APOE4, TDP-43, Lewy bodies, and hippocampal sclerosis, and the rarity and morphology of TDP-43 lesions what is clear contrast to what is typically observed in Alzheimer's disease of the old. Besides slow progression of memory impairment a slow evolution of behavioral and mood changes is not uncommon. Increased awareness of AD and non-AD clinical entities may ultimately help clinicians to establish timely clinical diagnose and to start an adequate/personalized therapeutic intervention.

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2. Warren JD, Fletcher PD, Golden HL. The paradox of syndromic diversity in Alzheimer disease. Nat Rev Neurol. 2012; 8:451-464.

3. Allen TA, Fortin NJ. The evolution of episodic memory. Proc Natl Acad Sci U S A. 2013;110(suppl 2):10379-10386

4. Daulatzai MA. Neurotoxic saboteurs: straws that break the hippo's (hippocampus) back drive cognitive impairment and Alzheimer's disease. Neurotox Res. 2013; 24:407-459.

5. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011; 7:263-269.

6. Schneider JA, Aggarwal NT, Barnes L, Boyle P, Bennett DA. The neuropathology of older persons with and without dementia from community versus clinic cohorts. J Alzheimers Dis. 2009; 18:691–701.

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8. Josephs KA, Murray ME, Tosakulwong N, et al. Tau aggregation influences cognition and hippocampal atrophy in the absence of beta-amyloid: a clinico-imaging-pathological study of primary age-related tauopathy (PART). Acta Neuropathol 2017; 133:705–715.

New insights in Fronto-Temporal dementia

Alessandro Padovani, Barbara Borroni
University of Brescia, Brescia, Italy

Frontotemporal Dementia (FTD) is a neurodegenerative disorder which asymmetrically affects the frontotemporal lobe, characterized by behavioural abnormalities, language impairment, and deficits of executive functions. Genetic studies identified mutations causing the disease, namely Microtubule Associated Protein Tau (MAPT), Granulin (GRN) and chromosome 9 open reading frame 72 (C9orf72) mutations, which contributed to elucidate the molecular pathways involved in brain depositions of either Tau or TAR DNA-binding protein 43 (TDP43) inclusions. However, in the majority of sporadic FTD patients, the mechanisms triggering Tau or TDP43 protein deposition are still to be uncovered. A co-autoimmune aetiology has been hypothesised. In a recent study aimed at defining the pathogenetic role of anti-AMPA GluA3 antibodies in FTD, .serum and cerebrospinal fluid (CSF) assessed and and the effect of CSF with and without anti-GluA3 antibodies was tested in rat hippocampal neuronal primary cultures and in differentiated neurons from human induced pluripotent stem cells (hiPSCs). One forth FTD sera were positive for the presence of anti-GluA3 antibodies and FTD patients with anti-GluA3 antibodies more often presented presenile onset, behavioural variant FTDwith bitemporal atrophy. Incubation of rat hippocampal neuronal primary cultures with CSF with anti-GluA3 antibodies led to a decrease of GluA3 subunit synaptic localization of the AMPA receptor (AMPAR) and loss of dendritic spines. In conclusion, autoimmune mechanism might represent a new potentially treatable target in FTD and might open new lights in the disease underpinnings.

Dementia in progressive supranuclear palsy and corticobasal syndrome

Zvezdan Pirtošek
University Hospital Centre Ljubljana, Ljubljana, Slovenia

Progressive supranuclear palsy (PSP) and Corticobasal degeneration (CBD) are progressive neurodegenerative parkinsonian disorders, the former characterized additionally by early falls and a supranuclear downward gaze palsy and the latter by progressive asymmetrical rigidity and apraxia. Initially only the movement disorder had been emphasized, but now the cognitive symptoms (dementia) are considered common. Differential diagnosis in early stages can be difficult; less than two-thirds of patients with pathologically proven PSP and only half of patients with CBD are diagnosed during life.

In PSP, the main pathologic targets are the diencephalon, brainstem, and frontal lobes and in CBD, the neocortex, the basal ganglia and the limbic lobe. Characteristics of cognitive impairments and dementia reflect this pathological distribution. PSP and CBD, similar to Alzheimer's disease (AD) are both tauopathies and

the molecular biology of tau protein is similar in PSP and CDB - 2 major isoforms of tau in contrast to AD, which shows three isoforms. Pathologically and clinically, dementia in CBD overlaps with PSP and both of them with PPA and FTD and may represent parts of the spectrum of a more common age-related neurodegenerative disorder, presenting as movement disorder and dementia.

Although acetylcholinesterase inhibitors and N-Methyl-D-aspartate receptor antagonists have been used off-label in PSP and CBD, there is little evidence that they are effective and risk of adverse effects may be considerable, such as worsening of frontal symptoms. A randomized, double-blind, placebo-controlled trial of donepezil in patients with PSP showed improvement in cognition but also reported a deterioration in ADL and mobility. Atypical antipsychotics for behavioural symptoms are not recommended as they increase mortality and may worsen Parkinsonism.

Dementia in Lewy body dementia and Parkinson's disease

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

Dementia is a frequent but often unrecognized problem in advanced stages of Parkinson disease (PD). Usually, PD is consider as mostly a motor disease, but non-motor symptoms are influencing the quality of life the most and they are the most important reason for institutionalization of PD patients. The point prevalence of dementia in PD patients is around 30% and around 10% of a PD population will develop dementia per year. Risk factors studied so far are: higher age, more severe parkinsonism, in particular rigidity, postural instability and gait disturbance, and mild cognitive impairment at baseline; and also male gender, education, depression, visual hallucinations can influence on that. There are a lot of different biomarker studies (from laboratory to novel structural and functional imaging techniques) trying to predict pre-dementia stages of cognitive impairment in PD, when we can try with researching of some neurprotective treatments. We know about limbic and cortical spread of Lewy pathology. There are known role of low cerebrospinal fluid levels of amyloid-β42, the APOE*ε4 allele, GBA mutations and SCNA mutation. Dementia can be seen in familial forms of PD such as PARK1 and PARK8.

Lewy body disease (LBD) is a neurodegenerative disease resulting in dementia. It is the second most common neurodegenerative dementia after Alzhemer's disease and the most common neurocognitive disorder with Lewy bodies, but still often unrecognized. Incidence of Lewy body dementias is 5.9 cases per 100,000 person-years. It shares clinical, genetic, neurochemical, morphological and pathological features with Parkinson disease (PD), the most frequent synucleinopathy, Parkinson disease dementia (PDD) and also have unknown etiology. Both are characterized morphologically by widespread cortical and subcortical α-synuclein/Lewy body plus β-amyloid and tau pathologies. Even though the diagnostic criteria for these neurodegenerative diseases are clearly established, and recently revised for LBD, their clinical diagnosis is often difficult. The clinical features of DLB and PDD include cognitive impairment, parkinsonism, visual hallucinations, and fluctuating attention. Despite considerable clinical overlap, their diagnosis is based on an arbitrary distinction between the time of onset of motor and cognitive symptoms: dementia often preceding parkinsonism in DLB and onset of cognitive impairment after onset of motor symptoms in PDD. Previus studies have shown more pronounced cortical atrophy, elevated cortical and limbic Lewy pathologies (with APOE ε4), apart from higher prevalence of Alzheimer pathology in DLB than PDD. These changes may account for earlier onset and greater severity of cognitive defects in DLB. Clinical management of both disorders includes cholinest-

erase inhibitors, other pharmacologic and nonpharmacologic strategies. Currently, no disease-modifying therapies are available.
In conclusion, although these disorders overlap in many aspects of their presentations and pathopsysiology they differ in other elements such as timing of cognitive behehavioral and motor symptoms, medications response, and neuropathological contributions.
In this article and lecture we review the current status of knowledge regarding cognitive impairment and current understanding of dementia and overlapping symptoms in PDD and LBD. This should help clinicians to suspect LBD and PDD at an earlier stage and provide better patient care.

Prion associated dementia

Fran Borovečki
University Clinical Center Zagreb, Zagreb, Croatia

Prions are small protein aggregates exhibiting a self-replicating feature and have been recognized as the causative factor in several neurological diseases. Human prion diseases are characterized by progressive neruodegeneration coupled with spongiform change of the neuropil and deposition of disease-associated proteins. Although much attention has been given to the transmissible form of the disease, majority of the cases are sporadic in nature, with a proportion of cases exhibiting a clear genetic background. Prion diseases are a known cause of dementia, especially in younger patients, marked by a swift cognitive and somatic decline, usually leading to a lethal outcome in a short period of time after initial diagnosis is established. Much attention has been attributed to the observations that misfolding of endogenous proteins in other neurodegenerative disorders, such as Alzheimer's and Parkinson's diseases, can lead to proteinaceous seeds, serving as self-propagating agents leading to the progession of the disease. Current body of knowledge shows that, although studies in humans and animal models show cell–to-cell transmission of disease-associated proteins in several neurodegenerative disorders leading to dissemination of pathological protein aggregates, prions remain the only proven proteinaceous agents to directly cause neurodegenerative pathological changes.

Multiple sclerosis and cognitive problems

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 cause of MS is unknown. The age at onset and diagnosis of MS is usually between 20 to 40 years of age, but symptoms may occur at both earlier and later phases of life. The global prevalence of MS is estimated to be around 2.5 million people, with a very uneven geographical distribution. The areas with the highest prevalence of MS are found in Europe and North America. Several recent studies from various countries have reported an increase in both incidence and prevalence of the disease. 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 dif-

ferent individuals, including sensory and motor disturbances, sometimes making the patient wheel chair bound, problems with vision, bladder, coordination and speech. During the latest decades, so called "invisible symptoms" and previously usually neglected complaints of pain, depression, fatigue and cognitive impairment have been highlighted as important symptoms of MS. The improved techniques of magnetic resonance imaging have revealed frequent and progressive cortical lesions in MS, a disease previously considered to be a white matter disease. The findings of progressive brain volume loss in MS have increased the interest in a evaluating the degenerative component of the disease. The neurologists accuracy of predicting cognitive impairment during an usual clinical visit is limited. Several batteries of neuropsychological tests have been presented to capture cognitive impairment, but unfortunately several of them have been too extensive and time-consuming to be of practical value in the busy clinical setting. At present, the symbol digit modality test (SDMT) is considered by many to be useful as a first hand test, since it is easy and rapid to administer and has shown good sensitivity. Objective neuropsychological findings show cognitive dysfunction in 45-70% of the patients with MS. Cognitive problems may occur early in the disease course and have been described in approximately 50% of patients with the first clinical manifestation of MS, clinical isolated syndrome, CIS. The most common cognitive symptoms in MS include slowed information processing, impaired short term memory and attention deficits. Longitudinal studies have shown a decline in cognitive function over the disease course, eg information processing has been followed over 8 and 17 years. The concurrent occurrence of depression and fatigue, both common symptoms of MS, may be confounders when evaluating the cognitive functions in a person with MS. Fatigue is one of the most debilitating symptoms in MS and may interfere with social activities. Fatigue is subjective and sometimes difficult to evaluate. Fatigue, depression and anxiety have been found to be strong predictors of self reported cognitive concerns. When evaluating the complete picture of cognitive problems in MS, it is also of importance to evaluate the possible influence of comorbid diagnoses and medication. The available disease-modifying treatments of MS have usually not focused on evaluating cognitive problems during the pivotal studies and no medication is approved for specific treatment of MS-related cognitive decline. It can be expected that cognitive problems in MS will become an area of increased research activities in the years to come.

Vascular dementia

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

Vascular dementia is one of the most common causes of dementia after Alzheimer's disease, causing around 15% of cases. Vascular dementia is the most severe form of vascular cognitive impairment that by definition compromise alterations in cognition, ranging from subtle deficits to full-blown dementia, attributable to cerebrovascular causes. Advanced age is a powerful risk factor for vascular cognitive impairment, and the prevalence and incidence of cognitive impairment increases exponentially after age 65. After advanced age recurrent stroke is second the strongest predictors of dementia onset. Vascular cognitive impairment stem from a wide variety of cardiovascu-

lar and cerebrovascular pathologies and it is generally thought that cognitive impairment results from the brain dysfunction caused by cumulative tissue damage. Despite the fact that vascular dementia is often encountered there is still a lot of uncertainties over disease classification and diagnostic criteria, controversy over the exact nature of the relation between cerebrovascular pathology and cognitive impairment, and the paucity of identifiable tractable treatment targets although recent work has led to a substantially improved understanding on how vascular brain injury affects cognition. Preventing vascular injury remains a promising approach to reduce the global burden of dementia, but additional efforts are needed to define the optimal strategy for prevention and develop efficient symptomatic treatments.

PET and SPECT in neurodegenerative dementias

Maja Trošt[1,2]
[1]University Medical Center Ljubljana, Ljubljana, Slovenia
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Structural and functional brain imaging has greatly improved our understanding of neurodegenerative brain diseases, and increased the clinicians' diagnostic and differential diagnostic accuracy. Imaging biomarkers of the most common neurodegenerative dementia due to Alzheimer's disease (AD), are now incorporated in clinical diagnostic criteria for the early diagnosis of AD and for the prediction of progression from mild cognitive impairment to AD.
Functional and molecular nuclear neuroimaging with SPECT and PET in AD has been used for the *in vivo* evaluation of various metabolic and biochemical alterations in the brain. Imaging with fluorodeoxyglocose (FDG) and PET shows us the state of tissue by measuring the regional anomalies at the synaptic level. It is an effective and safe modality to identify diagnostic patterns of glucose hypometabolism in neurodegenerative dementias. It is an effective and useful adjunct to other diagnostic information in the assessment of patients with progressive cognitive impairment.
Amyloid PET ligands enable the detection and quantification of amyloid neuritic plaques in the living human brain. It has a great potential as a diagnostic tool. Similar to FDG PET, it is now an established technique with data incorporated in the most recent consensus guidelines for the diagnosis of AD and predementia AD -related conditions.
Imaging the tau protein with PET and tracers that bind to tau protein is the newest imaging diagnostic tool in dementia. Currently, it is only used in the research settings. The recent studies have shown that functional and molecular nuclear neuroimaging has a strong impact on patients' management and also on caregivers' wellbeing.

Clinical management of Rett Syndrome

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Rett syndrome is a neurological disease caused by a defective protein involved in the transcription of methylated DNA and it affects almost exclusively girls. The causative gene is the methyl CpG-binding protein2-gene (MECP2) located on the X-chromo-

some. The current advances in DNA diagnostics are now also more common with MECP2 mutation in surviving males. The pathology of Rett syndrome differs from other disorders with intellectual disability. Some of the most distressing features of this unique disorder will be discussed. The disturbances in autonomic function are related to immaturity of brainstem autonomic centers resulting in hypersensitivity to sympathetic stimuli with insufficient parasympathetic control. Non- epileptic paroxysms are even more frequent in this syndrome than epilepsy. New insights into the brainstem phenomena have led to the neurophysiologic delineation of three cardiorespiratory phenotypes: forceful breathers, feeble breathers and apneustic breathers each demanding a specific approach. Comprehensive life-long management of Rett syndrome can significantly improve the health and longevity of affected individuals. Management is optimized by the involvement of a multidisciplinary team consisting of many different medical and paramedical specialists and an individualized approach at every age.

Rare genetic variants: patients with dementia and population

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Dementias present increasingly important public health and socioeconomic issue. Alzheimer's disease (AD), vascular dementia, dementia with Lewy bodies, and frontotemporal dementia (FTD) comprise most common types of dementia, with AD being most frequent as it accounts for 70% of all dementia cases. While it is expected that the prevalence will triple by 2050, there is a proportion of dementia patients with important genetic component.
Symptoms and signs of disease are not specific for dementia type and genetic forms are clinically indistinguishable from sporadic ones. Due to the clinical and genetic heterogeneity of dementias and lack of powerful genetic diagnostic tools, clinical diagnosis is still challenging and genetic epidemiology is hard to estimate.
Recently, next generation sequencing technologies emerged as an advanced tool for diagnosis of genetically heterogeneous disorders. We have systematically applied the technology for the diagnosis of patients with dementia, suspected to have genetic etiology. We were able to identify genetic etiology in about third of the patients examined.

Furthermore, we analyzed the Slovene Genomic database for the frequency of rare genetic variants in genes associated with monogenic genetic predisposition in Slovenian population to better understand the genetic epidemiology of dementia.