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

20th Symposium

1st RIJEKA FORUM ON NEURODEGENERATIVE DISEASES

Endorsed by Associations
Parkinson i mi and Neurodeg

17th October 2017.
9,00 am
University Campus Rijeka, University Departments, Lecture hall O-030,
Radmile Matejčić 2, Rijeka

P R O G R A M
OPENING
(9,00 – 09,15)

Introduction

Daniel Rukavina, M.D., PhD., Professor, 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

---

9,15 – 10,45 h

I. PARKINSONISM

Chairmen: Zvezdan Pirtošek and Tomas Revesz

Vladimira Vuletić, M.D., PhD, Clinical Hospital Center Rijeka, Rijeka
What we know about Parkinson's disease 200 years from first description?

Zvezdan Pirtošek, M.D., PhD, University Medical Centre Ljubljana, Ljubljana, Slovenia
Atypical parkinsonism

Tamas Revesz, M.D., PhD, University College London, London, UK
Clinicopathological correlations of atypical parkinsonism

Coffee break: 10,45 – 11,15

11,15 – 12,45 h

II. DEMENTIAS

Chairmen: Vida Demarin and Nenad Bogdanović

Nenad Bogdanović, M.D., PhD, Karolinska Institute, Stockholm, Sweden
Neurodegenerative dementias: clinical perspective

Tamas Revesz, M.D., PhD, University College London, London, UK
Diagnosing neurodegenerative dementias: the neuropathologist's perspective

Vida Demarin, M.D., PhD, Croatian Institute for Brain Research, Zagreb
Vascular dementia - is it possible to prevent?

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

13,30 – 14,30 h

III. MULTIPLE SCLEROSIS

Chairmen: Sten Fredrikson and Vladimira Vuletić

Sten Fredrikso, M.D., PhD, Karolinska Institute, Stockholm, Sweden
Multiple sclerosis in a time of changing ideas about symptoms, diagnosis and patho-physiology

Ingrid Škarpa Prpić, M.D., PhD, Clinical Hospital Center Rijeka, Rijeka
Is multiple sclerosis neurodegenerative disease?

Coffee break: 14,30 – 15,00

15,00 – 17,00 h

IV. GENETICS, NEUROIMAGING AND ANIMAL MODELS

Chairmen: Miljenko Kapović and Borut Peterlin

Nada Starčević Čizmarević, M.D., PhD, Clinical Hospital Center Rijeka, Rijeka
Genetics in MS

Borut Peterlin, M.D., PhD, University Clinical Center Ljubljana, Ljubljana, Slovenia
Genetics in neurodegenerative diseases

Zoran Rumboldt, M.D., PhD, Medical Faculty of South Carolina, Charlestone, USA
Magnetic resonance imaging in neurodegenerative diseases

Ivana Munitić, M.D., PhD, Department of Biotechnology, University of Rijeka, Rijeka
Animal models of amyotrophic lateral sclerosis

17,00 – 17,15 h

V. PANEL DISCUSSION AND CLOSING
Moderator: Vladimira Vuletić

What we know about Parkinson's disease 200 years from first description?

Vladimira Vuletić
Clinical Hospital Center Rijeka, Rijeka, Croatia

James Parkinson, who was an English surgeon, apothecary, geologist, palaeontologist and political activist, published his thin monograph titled An Essay on the Shaking Palsy1 exactly 200 years ago, in 1817, and this account represents the first description of Parkinson disease (PD) as a neurological disorder. Since the first formal description of Parkinson, our understanding of this common neurodegenerative disorder has expanded at all levels of description, from the delineation of its clinical phenotype to the identification of its neuropathological features, neurochemical processes and genetic factors. Along the way, findings have led to novel hypotheses about how the disease develops and progresses. Neuronal loss in the substantia nigra, which causes striatal dopamine deficiency, and intracellular inclusions containing aggregates of αsynuclein are the neuropathological hallmarks of Parkinson disease. The underlying molecular pathogenesis involves multiple pathways and mechanisms: αsynuclein proteostasis, mitochondrial function, oxidative stress, calcium homeostasis, axonal transport and neuroinflammation.Parkinson disease (PD) is the second-most common neurodegenerative disorder manifesting the hallmark features of Tremor, Rigidity, Akinesia/bradykinesia and Postural disturbances, comprising the acronym known to most medical students, TRAP. Beside these motor symptoms, many existing non-motor symptoms influence quality of life the most. PD affects 2–3% of the population ≥65 years of age, but 1 of 10 newly diagnosed patients is younger than 50 years.

Recent research into diagnostic biomarkers has taken advantage of neuroimaging in which several modalities, including PET, single-photon emission CT (SPECT) and novel MRI techniques, have been shown to aid early and differential diagnosis. Treatment of Parkinson disease is anchored on pharmacological substitution of striatal dopamine, in addition to non-dopaminergic approaches to address both motor and non-motor symptoms and deep brain stimulation for those developing intractable lDOPA-related motor complications. Experimental therapies have tried to restore striatal dopamine by gene-based and cell-based approaches, and most recently, aggregation and cellular transport of αsynuclein have become therapeutic targets. One of the greatest current challenges is to identify markers for prodromal disease stages, which would allow novel disease-modifying therapies to be started earlier. Nowadays, individuals with PD live longer, healthier lives thanks to a wealth of discoveries that led to more effective therapeutic strategies.These developments ant new treatments methods have given many new faces to PD. The introduction of levodopa provided miraculous control of the classical clinical features but resulted in a new face of motor fluctuations and dyskinesias. It also permitted the clear recognition of the non-dopaminergic features with another face of PD arising in the later stages, one now dominated by dementia as well as other treatment-resistant motor and non-motor problems. This face has been further refined in patients receiving advanced therapies (DBS, infusion therapies) in whom the classical dopaminergic motor features are minimally evident. The recognition that the disorder is clinically and potentially pathogenetically heterogeneous also forces us to further consider subtle differences in the facial characteristics of distinct Parkinson's diseases. Finally, the recognition of long-standing prodromal disease and the prospect of being able to reliably diagnose this in the future, long before any of the TRAP features become evident, promises to give a very new and different face to the disorder, one which has little or no recognizable relationship to the cases described by James Parkinson. We can be hopeful that advances in diagnosis and management in future will eliminate the earlier faces of the disorder that now compromise so much the quality of life. In this review will be present the fascinating 200year journey of PD research.

Atypical Parkinsonisms

Zvezdan Pirtošek [1, 2]
[1] Medical faculty, University of Ljubljana, Ljubljana, Slovenia
[2] University Medical Centre, Ljubljana, Slovenia

Atypical parkinson's (AP) is a general term used to describe syndromes manifesting with classical signs of parkinsonism (brady/hypokinesia, tremor, rigidity, postural impairment) but being conditions therapeutically and pathologically distinct from idiopathic parkinsonism or Parkinson's disease (PD).

In the life, the diagnosis is a clinical one; confirmation is by autopsy, pathological. However, there are several supportive instrumental investigations (imaging, testing of autonomic nervous system). The most important 'red flag' to differentiate atypical parkinsonisms from PD is (i) unresponsiveness to levodopa, the others being: (ii) symmetrical nature of symptoms & signs; early in the development of disease problems with (iii) balance, falls and/or freezing of gait, (iv) cognitive problems, (v) autonomic impairment, (vi) speech, (vii) swallowing and (viii) visual (oculomotor) problems.

Main groups of atypical parkinsonism include neurodegenerative disorders (atypical parkinsonisms in the *narrow* sense) and secondary & parkinsonisms as part of other neurological diseases (atypical parkinsonisms in *broad* sense).

(i) *neurodegenerative disorders* (Lewy body disease, multiple system atrophy, progressive supranuclear palsy, coticobasal degeneration)

(ii) *secondary parkinsonisms*: drug induced parkinsonism, vascular parkinsonism. parkinsonism due to repetitive brain injury, parkinsonism due to toxin exposure such as carbon monoxide poisoning, exposure to manganese, lead, cobalt or mercury; normal pressure hydrocephalus)

(iii) *parkinsonisms as part of other brain disorders* (Wilson's disease, Huntington's disease, spinocerebellar degenerations…).

In the presentation, video case reports of atypical neurodegenerative parkinsonisms will be presented and discussed from the point of *con* and *pro*.

Clinicopathological correlations of atypical Parkinsonism

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

The term atypical parkinsonian syndromes describes a pathologically heterogeneous group of neurodegenerative disorders clinically characterized by parkinsonism, in addition to signs atypical for Parkinson's disease such as pyramidal tract signs, myoclonus, supranuclear gaze palsy, apraxia, cerebellar ataxia, early autonomic dysfunction or early dementia. The group of atypical parkinsonism includes diverse disease entities such as progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), multiple system atrophy (MSA) and dementia with Lewy bodies (DLB).

PSP and CBD are sporadic, 'primary' tauopathies and both diseases are characterised pathologically by neuronal and glial inclusions composed of abnormal, hyperphosphorylated (4-repeat) tau. Evidence also suggests that the two diseases share genetic risk factors. Despite the similarities, there are robust neuropathological differences in the tau pathology between the two conditions (for example tufted astrocytes in PSP and astrocytic plaques in CBD), which allow a specific morphological diagnosis to be made. Clinicopathological

studies have also demonstrated different subtypes of PSP and CBD with characteristic clinical presentation and neuropathological findings.

MSA is a primary degenerative disease of the nervous system that is neuropathologically defined by the presence of cellular inclusions occurring predominantly in oligodendrocytes (glial cytoplasmic inclusions or GCIs). Although patients with parkinsonism (MSA-P) may show a preponderance of pathology in the striatonigral system while patients with predominant cerebellar signs (MSA-C) may have the principal pathology in the olivopontocerebellar system with variable striatonigral degeneration, an equal involvement of the striatonigral and olivopontocerebellar systems is the most common neuropathological variant. In all varieties of MSA there is usually involvement of the autonomic nervous system. Microscopically GCIs and neuronal cytoplasmic and nuclear inclusions occur extensively in MSA. The primary protein component of all types of inclusions, including GCIs is alfa-synuclein; hence MSA is defined as one of the synucleinopathies. The term DLB is used to describe a characteristic clinical syndrome with dementia, hallucinations, fluctuation in the level consciousness and parkinsonism. As in end stage Parkinson's disease with dementia (PDD), the neuropathology in most DLB cases is that of widespread cortical, subcortical and brainstem Lewy bodies, which are also composed of aggregated alfa-synuclein protein. A significant proportion of the cases also have some degree of Alzheimer-type pathology (amyloid plaques and neurofibrillary tangles). The implication of this is that an important interaction between Lewy- and Alzheimer-type pathologies has emerged in recent experimental and neuropathological studies in both DLB and Parkinson's disease dementia, emphasizing the significance of both types of pathologies in the progression of Lewy body disorders.

Neurodegenerative dementias: Clinical perspective

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

Dementia is a syndrome that is characterized by a state of cognitive impairment and is often associated with memory, language, executive and behavioral disturbances. To make a diagnosis of dementia requires that cognitive impairment is severe enough to affect an individual's functioning in daily life. A global study estimated that, in 2050, the worldwide prevalence of dementia will be around 100 million people, a double more than it is today. Dementia can be progressive and static. The most common cause of progressive dementia is the neurodegeneration, especially in the older population. A static dementia can result from a wide variety of causes including brain injury, congenital defect or a toxic-metabolic/hypoxic event. Mild cognitive impairment is distinguished from dementia by preserved functioning in daily life and often precedes neurodegenerative forms of dementia. Less common causes including infectious, autoimmune, paraneoplastic or toxic-metabolic often have a more subacute and even reversible course. The four most common forms of progressive dementias are Alzheimer's, Frontal lobe, Lewy Body and Vascular dementia.

Alzheimer's disease (AD) is the most common cause of dementia in the younger (<65) and older (>65) populations. The disease can be divided into two categories with respect to age of first clinical symptoms: early onset and late onset. Approximately 75% of AD is sporadic, with the remainder being inherited, and less than 5% has autosomal-dominant inheritance. Apolipoprotein E (*APOE*) is the major susceptibility gene for AD and can be associated with both early and late onset. The new clinical criteria published 2011 suggest that dementia is defined as cognitive impairment that impacts on at least two domains including acquiring and remembering new information, reasoning and handling of complex tasks, visuospatial

abilities, language functions, personality and behavior. There are two major presentations of AD, amnestic and non-amnestic. In most cases, the presentation is that of the amnestic version where the predominant deficits are impairment in learning and recall of recently learned information, with other domains of cognition being less affected. Non-amnestic forms of AD include corticobasal syndrome (CBS), frontal-variant AD, posterior cortical atrophy (PCA) and logopenic progressive aphasia (LPA). **Dementia with Lewy bodies (DLB)** represents a second major neurodegenerative disorder, accounting for 10–15% of autopsy proven cases of dementia. The clinical hallmarks of DLB consist of a progressive dementia associated with cognitive fluctuations, visual hallucinations and parkinsonism. In contrast to AD, those individuals with DLB have greater deficits in attention and visuospatial processing with relative preservation of memory and naming. The current criteria (updated 2017) require progressive cognitive impairment that interferes with normal social and occupational function. Of the three core features – fluctuations, visual hallucinations and parkinsonism – one is sufficient for a diagnosis of possible DLB and two for a diagnosis of probable DLB. **Frontotemporal dementia (FTD)** refers to a dementia syndrome in which the frontal and temporal lobes are predominantly affected. After AD, it is the second most common form of early-onset dementia. FTD can be clinically divided into two main categories, behavioral-variant FTD and Primary Progressive Aphasias (PPAs) that can be further subdivided in Agramatic-nonfluent (anPA) , semantic variant (svPA) and logopenic variant (lvPA). In approximately 10% of FTD, there is concomitant motor neuron disease. **Vascular Dementia** is a progressive cognitive deterioration of cerebrovascular diseases (CVD) that are related mainly to cerebrovascular occlusion and vascular bleeding leading to brain infarcts and hemorrhages. CVD can be presented alone or in combination with neurodegenerative diseases in aged people, contributing to the decline in behavioral, cognitive, emotional, sensory and motor functions.

Making a dementia diagnose accurate, depends on several assessment techniques that are mandatory to be performed such as neuropsychological testing, CSF biomarkers analysis, structural imaging by CT/MRI, functional recording (EEG), metabolic imaging by PET-FDG and molecular imaging such as PET-Amyloid camera. Each of mentioned dementia conditions has a characteristic finding using those techniques that make process of determining what is a the cause more accurate and easier. The treatment of those dementia conditions is symptomatic but still can make a difference for patients and caregivers especially if treatment is personalized. There is a hope that a current investigational substances in the latest stage of clinical development may substantially modify the disease progress.

Diagnosing neurodegenerative dementias: the neuropathologist's perspective

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

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. As the underlying pathological changes determine the clinical presentation, several diseases may result in a similar clinical presentation, for example frontotemporal dementia and corticobasal syndrome, which may be caused by one of a number of diverse pathologies.

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 the term protein folding disorders. A proportion

of the neurodegenerative dementias have a genetic cause. The most common risk factor for sporadic protein folding disorders is age. Genome-wide association studies have also demonstrated genetic variants which carry an increased risk for developing sporadic neurodegenerative diseases such as Alzheimer's disease and frontotemporal lobar degeneration with TDP-43 inclusions, Parkinson's disease and progressive supranuclear palsy.

As pathologically altered proteins, characteristic for each disease or group of diseases, form extracellular deposits or intracellular inclusions in neurons and in some instances, also in glia, these protein aggregates provide a valuable tool in the everyday neuropathological diagnosis. Although the aetiology of the majority of 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.

Vascular Dementia – is it possible to prevent it?

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

Aging is often associated with some cognitive impairment. Greater population life expectancy is one explanation for increased incidence of cognitive impairment cases. A large number of people with cognitive impairment and dementia is becoming one of the most important medical and social problems worldwide. Therefore, prevention of cognitive impairment is an imperative. Dementia includes a heterogeneous group of disorders, the most common being Alzheimer's dementia (AD) and vascular dementia (VD). Because cerebrovascular disease can cause mild cognitive deficits that affect multiple cognitive functions, the term 'vascular' mild cognitive impairment (VaMCI) was proposed. Patients diagnosed with VaMCI are in transition towards Alzheimer's disease. Vascular cognitive impairment (VCI) encompasses all cognitive disorders associated with cerebrovascular disease, from developed mild cognitive deficits to dementia. VCI is a syndrome with evidence of clinical stroke or subclinical vascular brain injury, and cognitive impairment affecting at least one cognitive domain. The most severe form of VCI is VaD.

Most cardiovascular risk factors, such as hypertension, diabetes mellitus, hypercholesterolemia, atrial fibrillation, and smoking are not exclusively risk factors for VD, but also for AD. Early changes in the blood vessel wall can be detected by early ultrasound screening methods which allow us to detect changes before the disease becomes clinically evident. Early disease detection enables in-time management, and studies have shown that careful control of vascular risk factors can postpone or even reverse disease progression.

Results of recent studies have shown that one third of dementia may be preventable with lifestyle change pointing out the necessity for being ambitious about prevention.

Multiple sclerosis in a time of changing ideas about symptoms, diagnosis and pathophysiology

Sten Fredrikson [1, 2]
[1] Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden
[2] Karolinska University Hospital Huddinge, Stockholm, Sweden

Multiple sclerosis (MS) has previously for many years been considered to be a T-cell driven autoimmune disease. During recent years this view has been questioned and new pathophysiological concepts have been suggested. One major new aspect that has been high-lighted

is the degenerative mechanisms that are active during early phases of the disease course and causing brain atrophy. MS is now considered to be both a neuroinflammatory and a neurodegenerative disease. Whether the degeneration is representing a primary pathological mechanism or whether it is only secondary to the immune disturbances is still a matter of debate. The ongoing evaluation of the immune reactions in MS continue to show complex patterns, and recently the B cells have attracted more attention. No new MS-specific immunological test has evolved for diagnostic purposes. The most important diagnostic laboratory test is still the analysis of oligoclonal bands in the cerebrospinal fluid. From epidemiological studies, in a global perspective, it seems clear that the prevalence of MS is increasing.

Since the turn of the century we have seen three new sets of diagnostic criteria, mainly based on findings on magnetic resonance imaging (MRI) and aiming at establishing a diagnosis as early as possible and thus making early treatment initiation possible. A new set of diagnostic criteria is expected within the next year.

Regarding clinical symptoms in MS the previously often neglected "invisible" symptoms, eg cognitive dysfunction, fatigue, depression and pain, are now in focus. Cognitive dysfunction is reported to affect 45-70% of patients with MS and causing substantial practical consequences in daily life, in employment status etc. Another important clinical aspect that is attracting more attention is the progressive forms of the disease. The most important change in the management of MS is the introduction, constantly ongoing, of new therapies to modify the disease course. There are now several approved disease modifying therapies approved and several drugs are in pipe-line for approval. The future of MS research and management of patients with MS looks promising and exciting.

Genetics in multiple sclerosis

Nada Starčević Čizmarević

Faculty of Medicine, University of Rijeka, Rijeka, Croatia

Multiple sclerosis (MS) is a chronic neuro-inflammatory autoimmune disease arise from complex interactions of both environmental and genetic factors. Typical features for complex genetic diseases include modest heritability without a classic Mendelian mode of transmission and heterogeneity, which mean that variation in a large number of genes contributes to the overall susceptibility. Both human leukocyte antigen (HLA) and a broad spectrum of non-HLA genes have been implicated in the etiopathogenesis of MS. Identification of susceptibility genes has been a major challenge in the past decades. Single-nucleotide polymorphisms (SNPs) within the susceptible genes are appropriate variants able to shed light into the genetic predisposition for MS and over 200 SNPs have now been described. The risk alleles indicate variation in the regulation of gene expression, rather than protein variation, underpins genetic susceptibility. Gene/gene interactions, as well as epigenetic mechanisms, are also believed to play an important role for the pathogenesis of complex diseases. Furthermore, distinct forms of MS exist with different underlying genetic causes. Remains an open question which loci are involved in the initial pathogenic events or influence the development and progression of the disease. Drug efficacy is also affected by multiple genetic factors and significant clinical challenge in pharmacogenomics represents variability in response to disease-modifying therapies in patients with MS. Efforts to identify groups of relevant biomarkers are beginning to show associations with responses, but, based on current data, the routine use of pharmacogenetics in MS is not imminent. Even though we are still far from knowing the full set of genes influencing the pathogenesis of MS, considerable success has been made through linkage studies, candidate gene association studies and in the last decade through the genome-wide association studies (GWAS).

Genetics in neurodegenerative diseases

Borut Peterlin

Clinical Institute of Medical Genetics, University Medical Center Ljubljana,
Ljubljana, Slovenia

Genetic research in the field of neurodegenerative disorders has recently importantly contributed to the understanding of disease mechanisms and development of therapeutic approaches. Additionally, new genomic technologies are rapidly changing the clinical practice of neurology. There is an important challenge of recognizing rare genetic neurodegenerative syndromes either representing separate clinical entities (i.e. Huntington's Disease, Wilson's disease) or the small subset of common disorders (i.e. Alzheimer disease, Parkinson disease, ALS). Namely, establishing a diagnosis of genetic disorders is often linked to an end of long diagnostic odyssey, leading to better estimation of prognosis, treatment, prevention and quality of life. In addition to neurologists, other medical specialists involved in the evaluation and care of patients with neurodegenerative disorders including family doctors, psychologists, psychiatrists, have the important role of recognizing the potential genetic etiology of the disease. In case of suspected genetic etiology, it is recommended to refer patients to specialized genetic services for genetic counseling and diagnosis. New genomic technologies, like next-generation sequencing, have recently revolutionized the diagnosis of neurodegenerative disorders and significantly improved access to genetic testing and it's yield. The model of care and experience in genetic evaluation of patients with neurodegenerative disorders at Clinical Institute of Medical Genetics Ljubljana will be presented.

MRI in Neurodegenerative Diseases

Zoran Rumboldt [1,2,3]
[1] Faculty of Medicine, University of Rijeka, Rijeka, Croatia
[2] Medical University of South Carolina, Charleston, USA
[3] Telemedicine Clinic, Barcelona, Spain & Sydney, Australia

This review will cover imaging protocols and assessment, as well as characteristic features of dementia, parkinsonism, multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS). Radiological findings may support the diagnosis of specific neurodegenerative diseases and are sometimes necessary to confirm the diagnosis. In addition to early detection, MRI may be used to assess disease progression and is adopted in current clinical trials.

Coronal-oblique (T1-weighted) images are positioned perpendicular to the medial temporal lobe and hippocampus, the main structures involved in many forms of dementia. Transverse FLAIR images are used to assess global atrophy, white matter (WM) lesions and infarctions; T2-weighted sequence is particularly useful for detection of lacunar infarctions in the deep gray matter, which can be missed on FLAIR. $T2^*$-weighted images are necessary for visualization of microbleeds in cerebral amyloid angiopathy (CAA) and hypertensive microangiopathy. Diffusion imaging may be helpful in younger patients or in rapidly progressive neurodegenerative disorders (Diff Dg of vasculitis and Creutzfeldt-Jakob disease - CJD, respectively). Sagittal (T1-weighted) images should also be obtained (particularly useful for detection of progressive supranuclear palsy - PSP), frequently a 3D sequence will be performed and images then reconstructed in various planes.

CT is useful when contraindications prevent MRI scan or when the only reason for imaging is to rule out surgically treatable causes. PET imaging (most commonly with FDG) may allow for early diagnosis of Alzheimer's disease (AD) and Frontotemporal Lobar Degeneration (FTLD); its role may be expanding with additional and novel radiotracers.

Standardized imaging assessment includes: GCA and MTA scales, Koedam score for parietal atrophy, Fazekas scale for WM lesions, and search for strategic infarcts (in regions involved in cognitive function). Lacunar infarcts should be differentiated from perivascular spaces.

The typical findings are: AD - medial temporal lobe atrophy (MTA); Presenile AD - parietal atrophy, primarily of the posterior cingulum and precuneus, hippocampus can be normal; FTLD - (asymmetric) frontal lobe atrophy and atrophy of the temporal pole; Vascular Dementia - global atrophy, diffuse white matter lesions, lacunes and strategic infarcts.

Dementia may overlap with parkinsonism and neuroimaging is helpful in detection of atypical parkinsonian syndromes – primarily multisystem atrophy (MSA) and PSP, also corticobasal degeneration (CBD). MRI is usually unremarkable in Dementia with Lewy bodies. Huntington disease, Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencehalopathy (CADASIL), as well as CJD demonstrate characteristic patterns of MRI findings. Normal pressure hydrocephalus (NPH), while being a somewhat controversial topic, may show typical imaging features.

MS, in addition to white matter demyelinating lesions also affects the gray matter and leads to progressive atrophy of the brain. MRI is used for diagnosis and follow-up, which may include automated volumetric measurements.

MRI in patients with ALS may be very characteristic and essentially pathognomonic, however it may be overlooked due to its symmetric involvement of the corticospinal tracts.

Animal models of amyotrophic lateral sclerosis

Ivana Munitić

Department of Biotechnology, University of Rijeka, Rijeka, Croatia

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive adult-onset neurodegenerative disease, which primarily targets motor neurons, but can also appear in a disease continuum with other neurodegenerations, most frequently with frontotemporal dementia. Effective disease modifying therapies are unavailable, so ALS almost invariably leads to respiratory muscle paralysis and death within 2-5 years upon diagnosis. Sporadic ALS cases are by far more prevalent than familial, but they are pathohistologically and clinically indistinguishable. ALS is marked by an unusually large phenotypic and genetic heterogeneity, with mutations in dozens of different genes and risk factors being found thus far, but no clear link established between genetic and phenotypic makeup. Therefore, despite extensive genetic characterization, the disease pathogenesis is still elusive, and it is puzzling how can so many different mutations ultimately converge to the same outcome of motor neuron degeneration. This has prompted the generation of a number of mouse models that harbour human ALS mutations. In this talk, I will discuss the advantages and disadvantages of the current mouse ALS models and comment on their translational potential. In particular, classical models such as the first and best characterized transgenic mouse model harbouring toxic prion-like mutations in SOD1 will be compared to the emerging loss-of-function models targeting neuroprotective ALS genes. The classical transgenic models been shown to successfully replicate several hallmarks of human ALS, including intracellular protein aggregate formation and neuroinflammation, and have led to the discovery of the non-cell autonomous death of motor neurons, and detailed characterization of an indispensable role of microglia, astrocytes and oligodendrocytes in triggering neuronal death. However, these models have not been able to reproduce all aspects of human ALS, perhaps contributing to the failure of a large number of clinical trials for ALS. Therefore, a special focus will be on the emerging non-transgenic ALS models, including a model created by our group, which target endogenous neuroprotective proteins. It is expected that the optimization and more scrupulous use of the current mouse ALS models will be useful for designing new targeted therapies.