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Cerebrovascular Lesions in Pick Complex Diseases: A Neuropathological Study with a 7.0-tesla Magnetic Resonance Imaging

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Abstract

Introduction: Pick complex refers to a spectrum of diseases that have in common the presence of tau inclusions. The main neuropathological phenotypes comprise tau-frontotemporal lobar degeneration (Tau-FTLD), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). The present neuropathological study investigates their incidence of cerebrovascular lesions.

Material and Methods: seventy patients underwent an autopsy and post-mortem MRI. The brains consisted of 14 with Tau-FTLD, 22 with PSP, 6 with CBD and 28 controls, who had no history of a brain disease. A whole coronal section of a cerebral hemisphere, at the level of the mamillary body, was taken for the semi-quantitative evaluation of the small cerebrovascular lesions such as white matter changes (WMCs), cortical micro-bleeds (CoMBs), and cortical micro-infarcts (CoMIs). In addition the severity and the distribution of WMCs, CoMIs and CoMBs were examined with 7.0-tesla MRI on three coronal sections of a cerebral hemisphere.

Results: on neuropathological examination severe WMCs and more CoMBs are observed in Tau-FTLD, while the latter are also more frequent in CBD. The MRI examination shows that severe WMCs are present in the frontal sections not only of the Tau-FTLD but also to a lesser degree of the PSP and CBD brains.

Conclusions: severe WMCs and the increased number of CoMBs are to be related directly to the neurodegenerative process and do not represent additional cerebrovascular disease. The Pick complex diseases have in common a low incidence of real cerebrovascular lesions and a favourable vascular profile.

Mitigation of TDP-43 Proteinopathy in Mouse Models by Oral Administration of a Novel Semi-Synthetic Withanolide Targeting Nuclear Factor-kappaB Signaling

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Abstract

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by the progressive degeneration of motor neurons. A landmark was the discovery of trans-activation response DNA-binding protein of 43 kDa (TDP-43) as a major component of ubiquitinated inclusions found in most ALS cases. Some years ago, our group discovered that TDP-43 pathology is associated with deregulation of nuclear factor-kappa B (NF-kappaB) activity. This led us to investigate the effects of root extract of Withania somnifera (Ashwagandha), an herbal medicine with anti-inflammatory properties, in transgenic mice expressing a genomic fragment encoding human TDP-43A315T mutant. The oral administration of Ashwagandha in hTDP-43A315T mice ameliorated their motor and cognitive performance. Remarkably, the Ashwagandha treatment reduced the cytoplasmic mislocalization of hTDP-43 in spinal motor neurons and in brain cortical neurons of hTDP-43A315T mice and it reduced hTDP-43 aggregation. Based on the notion that withaferin A is a major inhibitor of NF-kappaB in extracts of Withania somnifera, we have tested a novel semi-synthetic analog of withaferin A called IMS-088 (obtained from Imstar Therapeutics inc) in transgenic mouse models of ALS/FTD expressing human mutant TDP-43G348C or TDP-43A315T. Oral intake of withanolide IMS-088 ameliorated the performance of mice expressing mutant TDP-43 in the novel object recognition and passive avoidance tests. Moreover, microscopy demonstrated beneficial effects of IMS-088 in mitigating TDP-43 pathology in cortical and spinal cord neurons of ALS/FTD mice. The attenuation of cytoplasmic TDP-43 levels by IMS-088 treatment is likely due to an induction of autophagy by IMS-088 as suggested by increased level of LC3B autophagy marker. To further analyze the brain neuronal protein expression profile, we have generated doubly transgenic mice co-expressing mutant hTDP-43 and a RiboTag construct under the control of a neuronal gene promoter. Immunoprecipitated ribosomes were assessed by a proteomics platform using mass spectrometry analysis. The results indicated that translational synthesis of neurofilament proteins was highly reduced (~4
folds) in mice with TDP-43 pathology. Oral administration of withanolide IMS-088 rescued abnormal translational alterations in neurons and it restored neurofilament protein synthesis which is impaired in the disease. The results are in line with previous reports of interactions between TDP-43 and neurofilament mRNA species. These findings suggest that inhibition of NF-kappaB signaling and ensuing induction of autophagy by withanolide IMS-088 should be considered as potential therapeutic approach to alleviate TDP-43 pathology in neurodegenerative disorders.

New Piperazine Multi-Action Drugs Prevent Neurofibrillary Degeneration And Amyloid Deposition, And Improve Memory in Animal Models of Alzheimer's Disease

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Abstract

Alzheimer's is a devastating dementing disease involving amyloid deposits, neurofibrillary tangles made of Tau protein and cognitive impairment. Current compounds in clinical trials target only symptoms or one of the two main pathological processes. Herein, we describe RPEL a potential drug candidate derived by substituting acetylcholinesterase-inhibitor anti-memory-loss drugs Tacrine on a N,N'-disubstituted piperazine anti-amyloid scaffold.

As hoped the resulting hybrid molecule reduced both the amyloid pathology and memory loss in Alzheimer-related mouse models after six months of treatment and moreover the Tau pathology was also reduced. In vitro also, the compound reduced the phosphorylation of Tau and inhibited the release of Aβ peptides while preserving the processing of other metabolites of the amyloid precursor protein (APP) that have protective effects.

In conclusion, we describe for the first time herein a novel multi-effect molecule that targets both the amyloid and cognitive functions in well-characterized mouse models of either amyloid or Tau pathology.

Identification of Dysregulated Neurotransmission in Dementia: Novel Approach

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Abstract

Diagnosis of dementia is mostly clinical. Because of subjective nature of clinical diagnosis, many patients are misdiagnosed. It results in patients not receiving proper treatment on time to slow down disease progression. It is therefore important to have a diagnostic technique that helps us make an early diagnosis. A novel neuroimaging technique that we recently developed could be useful. The technique called single scan dynamic molecular imaging technique (SDMIT) uses positron emission tomography (PET) to detect, map and measure dopamine released acutely during cognitive or behavioral processing. It exploits the competition between a neurotransmitter and its receptor ligand for occupancy of the same receptor site. In this technique after patients are positioned in the PET camera, a radio-labeled neurotransmitter ligand is injected intravenously and the PET data acquisition started. These data are used by a receptor kinetic model to detect, map and measure neurotransmitter released dynamically in different brain areas. Patients are asked to perform a cognitive task while in the scanner and the amount of neurotransmitter released in different brain areas measured. By comparing it with the data acquired in age-matched healthy volunteers during performance of a similar task, it is possible to determine whether a neurotransmitter release is dysregulated in the patients and whether the dysregulation is responsible for clinical symptoms. Finding of a significant dysregulation in neurotransmitter release would confirm diagnosis of dementia and it will also help in differentiating different kinds of dementia. Since this technique measures neurotransmitter released under conditions of cognitive stress, it can detect changes at a very early stage, when dysregulation of is not expressed at rest but manifests under conditions of cognitive overload.

Biography

Dr. Rajendra D. Badgaiyan, MD, is a psychiatrist and cognitive neuroscientist. He is the Chief of Psychiatry at South Texas Veterans Health Care System, San Antonio, Texas. Dr. Badgaiyan was awarded the prestigious Solomon Award of Harvard Medical School
Targeting Mitochondrial Dysfunction, Oxidative Stress, Inflammation and Autophagy Impairment to Halt Progression of Neurodegenerative Diseases Like Ad Using Ubisol Q10 and Natural Extracts

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Abstract

There has been an exponential increase in the number patients diagnosed with Alzheimer’s and Parkinson’s disease as number of elderly increases. Although the etiological factors triggering AD and PD are very different, they ultimately bring about neuronal death which is, most likely, executed by a common mechanism(s) including oxidative stress, mitochondrial dysfunction and stress, accumulation of misfolded proteins and defective organelles and impaired proteasome and autophagy mechanism. Currently, there are no effective treatments to halt the progression of these diseases. Some traditional natural extracts like ashwagandha may contain phytochemicals that can reduce inflammation and oxidative stress. Recently we have reported unprecedented efficacy of Ubisol-Q10 (Next Remedies Inc.) in protecting neurons in in vitro and in vivo models of neurodegenerative diseases. The formulation contains CoQ10 and PEG-α-tocopherol forming jointly water-soluble nanomicelles. We have confirmed bioavailability of this formulation in brain. A comprehensive behavioral analysis of transgenic animals (PD and AD mice models) fed with this formulation indicated significant improvement in motor activity in PD and long-term memory and emotional reactivity in AD models compared to untreated animals. These results were complemented with histochemical analysis that indicated significant protection of neurons in substantia niagra region in PD models, lower amyloid beta burden (plaques) and increased autophagy in AD mice. This treatment leads to the stabilization mitochondrial functions, decrease of oxidative stress in neuronal cells, increased autophagy and induction of pro-survival astroglial cells. It would be great if a combination of Ubisol Q10 and natural extracts, both as simple nutritional supplements, can be investigated for neuroprotective efficacy in these disease models. These combinatorial treatments could halt the progression of disease in AD and PD patients and can be taken over long period of time without any harm.

Oral Presentation

Pur-Alpha, Member of a Family of Evolutionarily Conserved Nucleic Acid-Binding Proteins with Adaptability for Mammalian Neurological Functions

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Abstract

Pur-alpha (Pura) is a member of the Pur protein family and has a highly conserved nucleic acid binding domain that is present at least three times in Pura of most mammalian species. Through this signature domain, Pura binds a specific guanine-rich Pur element represented as (G_{2-4}N_{1-3})_n where N (nucleotide) is not G. Early studies showed that Pura plays an important role during the cell cycle through its Pur domain 3 binding of proteins involved in cell cycle regulation. Overexpression of Pura in cancer cell lines inhibits the cell cycle at G1/S and G2/M checkpoints. In Pura knockout studies, the homozygous mice died shortly after birth with neurological and hematopoietic developmental defects. Pura has a role in AIDS through association with the HIV-1 TAT protein and stimulation of HIV-1 propagation. Association of Pura and Tat stimulates replication and transcription of JC virus in glial cells. JCV is the causative agent of progressive multifocal leukoencephalopathy, an opportunistic infection in AIDS. In neurons, Pura has been shown to accompany mRNA to dendritic sites of translation. Mutations in the PURA gene have been linked to neurological phenotypes. In neurological repeat expansion diseases, such as the C9orf72 (C9) amyotrophic lateral sclerosis (ALS)/frontotemporal dementia (FTD) disease spectrum, the G-rich sequence of the hexanucleotide repeat expansion (HRE) is a Pura binding element. Sequestration of Pura by the HRE has been proposed to be a factor in the pathogenesis of ALS/FTD. Overexpression of Pura in animal models mitigates neurodegeneration caused by the C9 HRE. We are currently testing peptides based on the Pur binding domain in regard
to their binding the C9 repeat sequence and ability to influence RNA secondary structure. The evolutionary conservation of the Pur domain indicates a role for its nucleic acid binding in survival of many species, and extends to neurological development in mammals.

**White Matter Damage in Alzheimer’s Disease**

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**Abstract**

Cerebral white matter damage (WMD), consisting of demyelination with/without axonal loss, is assumed to be associated with small vessel disease (SVD)-associated ischemia and supports a diagnosis of vascular dementia (VaD).

However, studies have suggested posterior WMD may also result from degenerative mechanisms secondary to Alzheimer’s disease (AD) pathology - with axonal loss occurring as a consequence of cortical atrophy or Wallerian degeneration. Our recent extensive quantitative pathological and biochemical study in parietal WM from human brains revealed that in AD, WMD was associated with both axonal and myelin loss, in contrast to non-AD cases, in which WMD was associated with myelin loss only. Wallerian degeneration-associated protein was significantly higher in AD and associated with increasing burden of AD pathologies. Furthermore, non-AD cases exhibited significantly higher levels of pre-mortem ischemic markers indicating that WM was mainly attributed to ischemia [1]. These are the first data to demonstrate a difference in the pathological and molecular composition of parietal WMD in AD suggesting an additional pathogenic mechanism.

Misdiagnosis of AD as VaD due to the presence of WMD is frequently observed at post mortem assessment: further elucidation of the pathogenesis of WMD is paramount for the accurate clinical diagnosis and accuracy of cohort stratification in clinical trials. Currently, the pathological and molecular composition of frontal WM is underway, which will inform us of any diagnostically relevant topographic differences in WMD, as well as lipidomic profiling of damaged WM for the elucidation of molecular lipid signatures that may have therapeutic relevance.

**Biography**

He is a Research Fellow from Newcastle University funded by the Alzheimer’s Society with an interest in neurodegenerative and cerebrovascular pathology in the aged human brain. His research focus is on the aetiology of white matter damage in Alzheimer’s disease and normal ageing, in which He implement post mortem MRI of fixed human brains to bridge the gap between clinical and neuropathological assessment. He is also involved in the development of methods for high throughput quantitative neuropathological assessment to aid research into the influence of multiple pathologies in the human brain.

**The Effects of Pollutants and Infection on Autism are Linked via the Aryl Hydrocarbon Receptor and by an Sappα/aβ Imbalance**

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**Abstract**

Gene-environment interactions were studied for 206 Autism susceptibility genes (ASGs: Autworks) in relation to chemicals (Comparative Toxicogenomics Database) and pathogens, using enrichment analysis. ASGs localized to placental, skin, intestinal and brain barriers and were targeted by multiple compounds implicated in autism (Tetrachlorodibenzodioxin, benzo(a)pyrene, polycyclic aromatic hydrocarbons, metals, valproate, acetaminophen, SSRIs, cocaine, bisphenol A, phthalates, polychlorinated biphenyls, flame retardants, diesel constituents, terbutaline and oxtotin and over 100 endocrine disruptors. These included food additive and cosmetics ingredients (Tretinoin, soy phytostrogens, aspartame, titanium dioxide and sodium fluoride) household products and multiple pesticides. Prenatal/childhood infection has been linked to autism and ASGs were also targeted by the host arm of 18 pathogen interactomes, mycotoxins and Toll-like receptor ligands. A microarray study from leukocytes of autistic toddlers also matched infection related datasets from the Broad Institute molecular signatures database. The levels of antimicrobial Aβ are decreased in autism while those of the trophic sAPPalpha are increased. This affects the excitatory/inhibitory balance in the autistic brain. Multiple ASG products regulate the Aβ/ sAPPalpha equilibrium and the reduction in antimicrobial Aβ coupled with increased
sAPPalpha might well explain the brain overgrowth and vulnerability to infection in autism.

Arylhydrocarbon receptor (AHR) activation is a common pathway linking infection and pollution. AHR is a pattern recognition receptor responding to bacterial pigments and activated by Dioxins, polycyclic aromatic hydrocarbons, other miscreants and by infection. Infection diverts tryptophan metabolism towards the kynurenine pathway, generating several endogenous AHR agonists including kynurenic acid. Pollution and infection control might well stem the autism epidemic.

Biography

After a degree in Zoology, He switched to Pharmacology (Leeds, Bradford and Bristol) ending up heading a Neuroscience genomics group at Synthelabo in Paris (now Sanofi). He is now retired and work from home using "Big data" publicly available on the web to analyse gene/environment interactions in silico in relation to neurological and psychiatric disorders.

He also curate a website (PolygenicPathways) recording genes and environmental risk factors related to these conditions. This also contains a number of host/pathogen interactomes.

Creutzfeldt-Jacob Disease: The Past Decade and a Half
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Abstract

Creutzfeldt-Jacob disease (CJD) is a rare, degenerative, and fatal brain disorder. Its prevalence is about one person in every one million per year worldwide. The symptoms are progressive mental deterioration and involuntary movements. CJD belongs to a family of human and animal diseases which is known as transmissible prion diseases. Diagnosis is difficult, and there is no effective treatment for this devastating disease.

We experienced one probable case of sporadic CJD in 2002. Diffusion weighted image (DWI) of brain MRI was not available back then, however patient displayed typical periodic synchronized discharge (PSD) in electro-encephalography (EEG). We administered Quinacrine for 90 days, however its effect was minimal. Sixteen years later, we had another patient who was diagnosed with possible CJD. Diffusion restriction on DWI was seen in the cortex, but no PSD was observed in EEG. We discuss the progress in diagnosis and treatment of CJD over the past decade and a half.

Biography

Yuko Harada, M.D. received her M.D. degree from the Keio University School of Medicine. Dr. Harada is currently Division Head of Internal Medicine at Yamato Tokushukai Hospital. From 2014 to 2017 she was Director of the Department of Internal Medicine at Shin-yurigaoka General Hospital. Until 2013 She was Vice Director of the Department of Cardiology at Kawasaki Municipal Ida Hospital, where she also completed her residency. Dr. Harada received the Chairman's Award from the Japan Endocrinology Association for her life-saving work on thyroid storm. She has authored numerous research papers in the pioneering fields of Internal Medicine, Cardiology, and Radiology.

Assessing the Effects of Damage Caused by Stroke on the Cells of The Neuro-Gliovascular Unit of The Brain in Relation to Dementia Onset
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Abstract

Background and objectives: Damage to the brain from impaired blood supply is an important cause of dementia. Around a quarter of stroke survivors develop progressive cognitive decline more than 3 months post-stroke. Impaired executive function, a characteristic of post-stroke dementia (PSD), is associated with pathology of the anterior cognitive circuits, but the pathoetiology of PSD remains unclear. This study aims to find novel pathways by which cell damage in the brain can give rise to PSD.

Methods: 10 control, 10 PSD and 10 post-stroke non-demented (PSND) cases from the Cognitive Function After STROKE (CogFAST) study were subject to laser capture microdissection to obtain astrocyte-, neuronal- and endothelial- rich RNA from frontal cortex and
white matter. Genechip microarray analysis was performed to identify differentially expressed genes between groups.

**Results:** Clear gene expression differences between the groups for all three cell types were identified. Compared to control cases, neurons isolated from PSD cases showed alterations in neuroprotective and neurotoxic pathways alongside changes in cellular breakdown and metabolism. Astrocytes showed altered calcium signalling, gene surveillance and fatty acid metabolism, while endothelial cells showed altered calcium signalling.

**Conclusions:** Analyses of the neuro-gliovascular unit of the frontal brain region shows pathway differences between PSD, PSND and control groups. For neurons, the major differences were between PSD vs either PSND or controls, suggesting that changes are associated particularly with dementia, rather than stroke per se. This study will extend the knowledge of the mechanisms by which cells are damaged in PSD and identify potential novel therapeutics.

**Biography**

Dr Rachel Waller, post-doctoral researcher, has worked in the neurodegenerative disease research field for the past 5 years since completing her PhD studies investigating the transcriptomic and proteomic profile of astrocytes in multiple sclerosis. Her first post-doctoral position investigated the potential role of microRNAs as biomarkers in motor neuron disease prior to studying the pathology of white matter lesions (WML) in the ageing brain. While continuing her work on WML, Rachel's current post-doctoral role involves assessing the effects of damage caused by stroke on the cells of the neuro-gliovascular unit of the brain in relation to dementia onset.

**Somali Woman with Multiple Sclerosis**

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**Abstract**

There is variable prevalence of multiple sclerosis, higher in those residing in latitude away from the equator, and among the Caucasian population. Multiple sclerosis has not been reported in some countries, partly related to access to modern medicine. There is no previous report of multiple sclerosis in the medical literature from Somalia or Somali diaspora. We report an adult Somali woman who has relapsing remitting multiple sclerosis for 8 years, affecting the optic nerves, cerebellum and spinal cord.

**Biography**

Consultant Neurologist with interest in Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorder. Have worked as Neurologist for 10 years in Department of Neurology, Hospital Kuala Lumpur. Vice chairperson of Neuroimmunology and Neuroinfection Council, President of Multiple Sclerosis, Manage the Multiple Sclerosis Clinic in Department of Neurology, Hospital Kuala Lumpur. Local Champion for Brain Health

**Multimorbidity in Aged Human Brains: Lessons from Quantitative Neuropathological Assessment**

Kirsty E. McAleese*, Lauren Walker¹, Mary Johnson¹, Paul Francis² and Johannes Attems¹

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**Abstract**

It is becoming increasingly clear that the ageing brain is characterized by the presence of multiple age-associated pathologies, i.e., hyperphosphorylated-tau (HP-T), amyloid-β, α-synuclein and cerebrovascular disease, rather than just the ‘pure’ characteristic neuropathological or vascular lesion. Recent preliminary data on over 900 donated human brains from Brains for Dementia Research (BDR) UK has revealed that of the neuropathological confirmed demented cases 57.6% exhibited at least one additional age-associated pathology, 13.2% exhibited two additional pathologies and 2.6% presented with three or more additional pathologies. Studies suggest that the presence of additional pathologies may lower the threshold for overt clinical dementia and an accelerated decline in cognition.

However, current diagnostic criteria employ semi-quantitative grading that masks subtle differences in pathological burden. Implementation of objective quantitative neuropathological assessment are required to allow for the detection of these subtle differences and their translatable impact on the clinical picture. We developed a Tissue microarray (TMA) system that enables quantitative assessment of 15 distinct regions from any given case on a large scale. Quantified data from 146 cases with semi-quantitative ‘severe’ levels of age-associated pathologies revealed HP-T varied up to 11-fold, amyloid-β varied up to 2.5-fold and α-synuclein varied...
up to 12.5-fold between cases. Quantitative data from TMA assessment highlight the range in pathological load across cases and is beneficial to further elucidate the heterogeneity of neurodegenerative diseases.

Deep Neural Networks for Healthcare Domain and Clinical Applications towards an Accurate Prediction of the Parkinson's disease status

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Abstract

Parkinson's disease (PD) is a long-term degenerative disorder of the central nervous system, with symptoms generally appearing slowly over time. Predicting the PD disease is critical as motor and non-motor manifestations occur many years after the onset of neurodegeneration, hence its early management of disease is a significant challenge in the field of PD therapeutics. While part of previous studies with respect to the prediction of Parkinson's Disease has been based mainly on brain images, dependencies between additional patients' information have not been taken into account. This observation suggests that prediction of Parkinson's Disease along with additional patients' data with a unified framework should outperform Machine Learning (ML) algorithms that treat different sources of patients' information separately. Our presented framework relies on Multi-Task Learning (MTL) implemented with Deep Neural Networks (DNNs) with shared hidden layers. Additionally, we discuss the lessons learned from our experimental settings with respect to addressing several research questions such as the importance of selecting the additional patients' information (i.e. sex, age) respectively, which is the best performing task combination to achieve such improved Parkinson's disease prediction, as well as whether all the different sources of patients' information (auxiliary tasks) are equally effective.

Biography

Dr. Aggeliki Vlachostergiou received her Ph.D. degree (with distinction) in Computer Science from the National Technical University of Athens (N.T.U.A.) in 2018. Prior to that, she received her M.Sc. degrees in Speech & Language Processing and in Image & Signal Processing from the University of Edinburgh and University of Manchester, U.K. in 2009 and 2012 respectively. Dr. Vlachostergiou was a visiting Research Assistant at the U.S. Army Research Laboratory (ARL) at the University of Southern California (USC) in L.A. during the summer of 2017. Her current research interests are positioned in the cross-section of the research areas of Interaction Context and Affective Computing, investigating if and how context is incorporated in automatic analysis of human behavior, through computational approaches that are applied in the healthcare domain. She has published articles in 2 international journals, 1 book chapter and 13 papers in international conferences and workshops.

Reliability and Accuracy of A New Laryngo-Pharyngeal Esthesiometer (LPEER) for the Exploration of the Laryngeal Adductor, Cough and Gag Reflexes Thresholds of the Upper Airway

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5Clinica Universidad de La Sabana, University of La Sabana School of Medicine, Chia, Colombia
6University of La Sabana, School of Engineering, Chia, Colombia

Abstract

Impaired laryngeal adductor reflex threshold (LART) during the Fiberoptic Endoscopic Evaluation of Swallowing (FEES) has been correlated with dysphagia severity, but the reproducibility of this test has been poor. Additionally, there are no clinical tests aimed at measuring the thresholds of the cough (CRT) and gag (GRT) reflexes of the upper airway. We performed a reliability and accuracy study of a new Laryngopharyngeal Esthesiometer (LPEER) capable of measuring the LART, CRT and GRT.

The reliability study included 67 subjects, evaluated by expert and novel raters, and the accuracy study included 118 subjects. All subjects were consecutive and prospectively recruited. FEES was the reference test. The order of the raters was randomly assigned; each rater performed two measurements on every patient and was blinded to the other rater's results. All subjects underwent the measurement of the right and left LART, CRT, and GRT, using the LPEER. Reliability was assessed by the Bland-Altman Plot and intraclass correlation coefficient (ICC). The accuracy was assessed comparing the LART, CRT and GRT against major alterations of
swallowing safety in FEESST, a ROC curve was constructed and the Area Under the Curve (AUC-ROC) was calculated.

Intra-rater ICC ranged from 0.90 to 0.98, inter-rater ICC ranged from 0.70 to 0.87. The AUC-ROC ranged from 0.71 to 0.85 to predict severe oropharyngeal dysphagia. Adverse events were mild.

LART, CRT and GRT measured using the LEER showed good to excellent reliability, discriminating capacity and accuracy to predict severe oropharyngeal dysphagia.

**Antiphospholipid Antibodies Overlapping in Isolated Neurological Syndrome and Multiple Sclerosis: Neurobiological Insights and Diagnostic Challenges**

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4 Department of Neurology, Hospital Clinico San Carlos, Madrid, Spain

**Abstract**

Antiphospholipid syndrome (APS) is characterized by arterial and venous thrombosis, pregnancy morbidity and fetal loss caused by autoantibodies directed against phospholipids (PL) involved in coagulation process. The isolated neurological APS represents a significant diagnostic challenge, as epidemiological, clinical and neuroimaging features may overlap with those of multiple sclerosis (MS). In MS, autoreactive B cells, autoantibodies, and CD8+ T cells play a dominant role in myelin degradation. We have thoroughly revised the scientific literature on patients diagnosed with MS, addressing the prevalence of non organ-specific antiphospholipid (aPL) autoantibodies, that could account for APS patients with MS-like syndrome. The reported prevalence was between 2%–88%, with major positivity for anti-cardiolipin and anti-β2glycoprotein1, and with predominant IgM over IgG isotype both in serum and CFS. Owing to the conflicting results reported by studies, pathogenic role and clinical significance of aPL antibodies in MS remain still unclear. The hypothesis is that aPL antibodies could have a role in worse or chronic CNS injury in MS, because their higher titer was reported during exacerbation or tardive MS clinical phases. Evidences suggest a not exclusively thrombogenic role for aPL antibodies, but also a potential direct link on astrocytes, neurons and cerebral vascular endotheliocytes, explaining brain manifestations in APS or MS. Nowadays, there are no definite diagnostic tools for atypical MS and neurological APS, but their proper diagnosis could allow a prompt anticoagulant treatment of APS, preventing/reducing APS-related morbidity and mortality. Also in MS, still an incurable neurodegenerative disease, early more targeted treatment will better control relapses, reducing accumulation of physical and neurological disability in the long-term.

**Physiological and Pathological Roles of Glycogen in Astrocytes and Neurons**

**Jordi Duran**1,2*, **Agnès Gruart**, **José M. Delgado** and **Joan J. Guinovart**1,2

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3 Division of Neurosciences, Pablo de Olavide University, Spain

**Abstract**

Although glycogen is present in the brain at much lower concentrations than in muscle or liver, it plays important roles in this organ. By characterizing an animal depleted of brain glycogen, we have shown that the polysaccharide plays a key role in learning capacity and in activity-dependent changes in hippocampal synapse strength. Strikingly, the lack of brain glycogen also makes these animals more susceptible to epilepsy. Since glycogen is essentially found in astrocytes, the diverse roles proposed for this polysaccharide in the brain have been attributed exclusively to these cells. However, we have demonstrated that neurons have an active glycogen metabolism that contributes to tolerance to hypoxia and to learning abilities.

In some conditions glycogen is abnormally accumulated in the brain. The most striking example of this is Lafora disease, a fatal neurodegenerative condition that starts as myoclonus epilepsy and proceeds to rapid cognitive deterioration and death. The hallmark of the disease is the presence in the brain of high numbers of glycogen aggregates, known as Lafora bodies. Our findings reveal that the accumulation of this aberrant glycogen accounts for the propensity to epilepsy and the neurodegeneration observed in models of the disease.
Our findings change the current view of the role of glycogen in the brain and reveal that endogenous neuronal glycogen metabolism is important in certain conditions and that glycogen accumulation contributes to neurodegenerative diseases.

**Biography**

After graduating in Pharmacy (1999) and Biochemistry (2002), in 2007 I obtained my PhD degree. In 2008 I joined Professor Joan J. Guinovart's team (IRB Barcelona) as a Postdoctoral fellow, being promoted to Research Associate in 2012. Our laboratory is devoted to the analysis of the physiological roles of glycogen, but also of the consequences of its accumulation in several diseases, particularly in the brain.

**Pharmacological Targeting of Alpha-Synuclein and Tppp/P25 In Parkinson’s Disease: Challenges and Opportunities in a Nutshell**

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**Abstract**

With the aging of society, neurodegenerative disorders such as Parkinson’s disease (PD) become more widespread and cause serious socio-economic problem. Currently there are only symptomatic therapies for PD, which can slow the progression of symptoms, but no disease-modifying treatment is available. The discovery and development of therapeutic strategies for synucleinopathies are limited by the lack of understanding of the exact pathomechanisms. The hallmark proteins of these diseases are alpha-synuclein (SYN) and Tubulin Polymerization Promoting Protein (TTPP/p25), the assembly of which is pathogenic and are formed at an early stage of the disease. These hallmarks are intrinsically disordered proteins with high conformational plasticity displaying both physiological and pathological functions; therefore, they are challenging drug targets. The endogenous SYN and TTPP/p25 occur in neurons and oligodendrocytes in normal brain, respectively; however, they are co-enriched and co-localized in both cell types leading to PD and multiple system atrophy. By exploiting the fact that the SYN-TPPP/p25 complex is formed exclusively at pathological conditions, we have established a new innovative strategy for the validation of a specific drug target. Namely, the interface of this pathological SYN-TPPP/p25 complex has been suggested as a specific antiparkinson drug target. The segments involved in the formation of the pathological interface have been identified and validated in vitro using human recombinant proteins and in living HeLa cells by immunofluorescence microscopy. These results may lead to the development of **peptidomimetic foldamers** suitable for pharmaceutical intervention.

**Neuroprotective Role of Kolaviron, A Natural Bioflavonoid, in Rotenone and MPTP Models of Parkinson’s Disease**

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**Abstract**

Parkinson’s disease (PD) is the most prevailing cause of neurological disorder and the second most common neurodegenerative disorder ranked after Alzheimer’s disease. It is characterized by gradual but progressive loss of dopaminergic neurons in both substantia nigra and striatum of the brain leading to disturbances in striatal circuitry function which majorly manifests in an array of physical symptoms including rigidity, muscle stiffness, resting tremor, bradykinesia, gait impairment and unsteady balance. Currently, the first line therapeutics has failed to address the progressive and degenerative aspects of PD hence the search for alternative naturally occurring agent. This study investigated the neuroprotective ability of kolaviron (KV), a natural antioxidant and anti-inflammatory biflavonoid from Garcinia kola seed to rescue striatal neuronal damage, redo-inflammation and behavioural impairment in rodent models of Rotenone (ROT) and MPTP PD disease. ROT elicited motor incompetence in rats attributed to enhanced striatal neurodegeneration, increased alpha synuclein formation and reduced tyrosine hydroxylase expression. ROT intoxication significantly increased reactive species production, and up-regulated COX-2 expression, enhanced myeloperoxidase activity and increased concentration of striatal inteleukine-6 (IL-6), IL-1β and tumour necrosis factor (TNF-α). Treatment with kolaviron reversed the rotenone-associated locomotor dysfucntion neurobiochemical imbalance, altered antioxidant defence system and neuroinflammation as well as improved capacity to maintain efficient gait with minimal rigidity and enhanced coordination. Similarly in mice, Kolaviron suppressed MPTP-mediated striatal oxidative stress, degeneration of striatal dopaminergic neurons,
reduced DJ-1 secretion and upregulated expression of caspase-3. Additionally, kolaviron facilitate cytoprotective antioxidant response and prevented MPTP-mediated neuroinflammation by blocking striatal infiltration of peripheral CD45R positive cells believed to constitute plasmacytoid dendritic cells. Our study provides evidence that the neuroprotective capacity of kolaviron to rescue striatal degeneration, behavioural impairment, antioxidant/redox imbalance and neuroinflammation implicated in the pathogenesis of PD may involve upregulation of DJ-1 secretion and inhibition of CD45R cells infiltration. Our data recommend kolaviron as a possible neuroprotective strategy in the management of Parkinson's disease and its treatment-related behavioural complications.

Keywords: Kolaviron, Rotenone, Neurobehavioural deficits, Striatal Redo-inflammation, tyrosine hydroxylase, MPTP, Striatum, DJ-1, CD45R, behavioural incompetence

A Human Cell Culture Model of Parkinson's Disease to Investigate the Relationship Between Iron Accumulation and Parkinson's Disease

Sebastien Farnaud and Kosha Mehta

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Abstract

With an estimated seven to ten million sufferers worldwide, Parkinson's disease (PD) is the second most common age-related neurodegenerative disorder. Progress in elucidating its causes has been slow, partly due to the lack of human-relevant models. Similarly, while the contribution of iron is increasingly advocated, identifying its role in disease progression remains challenging mainly due to the lack of valid model. In this study, we created Parkinson-like conditions in a human neuron model and conducted preliminary studies on iron-related parameters to assess whether these cells replicated iron accumulation observed in Parkinsonism. The differences observed in distribution of iron in our human model and with the expression of major iron-related proteins, indicate that our model reproduces successfully the disease state, and suggests that further study could help in advancing our understanding of PD.

Biography

Dr Sebastien Farnaud is Associate Professor at Coventry University and lead for enterprise and innovation in the Centre of Sport, Exercise and Life Sciences, where he leads a research group; his work on iron metabolism and his interest in human health have led him to develop human-relevant approaches to investigate physiological and metabolic aspects in neurological disorders. Other interests of his work include the analysis of gastrointestinal microbiota in relation to diseases and disorders, but also the development of antimicrobial peptides to palliate the ever growing antibiotic resistance to antibiotics.

Multiscale Computational Models of Neuronal and Network Dysfunction in Huntington's Disease

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Abstract

We demonstrate computational models of two electrophysiological phenotypes observed at different scales in Huntington's Disease R6/2 and Q175 mouse models. The first occurs at the network level of local field potentials in dorsal striatum of symptomatic animals, in which gamma band power is elevated. Exaggerated functional coupling between cortical delta wave fluctuations and episodic gamma events was demonstrated. We showed using a model of synaptically coupled, fast-spiking interneurons, that this elevated power depends on gap junctional coupling between model neurons, and that increased functional coupling depends on decreased cortical synaptic drive onto neurons. We propose such changes in network drive as compensatory for a second disease phenotype, observed at the cellular level, in which neuron excitability as measured by rheobase, membrane potential, and input resistance are strongly modified among in vitro preparations from the same mouse models. These modifications have been targeted for reversal in preclinical studies using a PDE10 inhibitor, and results supported the drug's further investigation in the Phase 2 Amaryllis trial by Pfizer, which failed in 2017. Using population-based optimization methods, we determine optimal virtual drug profiles for fully reversing these phenotypes, as well as retrospectively analyze what optimal target components may have been missed by the PDE10 inhibitor. We discuss how coupling these models might identify additional preclinical measures both in vitro and in vivo for consistently assessing new therapeutic compounds to treat Huntington's Disease.
Biography

James Kozloski is a Neuroscientist and collaborates with researchers worldwide in the fields of Computational Neuroscience and Cardiology, modeling brain and heart from synaptic plasticity in neural circuits to functionally active tissues in each. He is an IBM Master Inventor, and creator of the Model Graph Simulator, a high-performance computing tool that's been applied to Neural Tissue Simulation and Deep Learning on IBM’s Cloud and supercomputers. As manager of the Department of Multiscale Computational Modeling, James oversees efforts to merge AI and biophysical models. His team focuses on quantitative, systems solutions for model-based brain and heart disease therapeutic design.

The Benefit of IVIG in Neuroimmune Diseases Such As Autism and PANDAS/PANS

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Abstract

Research has shown that a subset of the Autism Spectrum Disorder population presents with immune dysregulation. To explore this topic further, we investigated the efficacy and tolerability of intravenous immunoglobulin (IVIG) infusion in children with ASD. In this study, participants were recruited based on a diagnosis of autistic disorder, Asperger’s disorder, or pervasive developmental disorder not otherwise specified. Participants also showed evidence of immune dysfunction based on abnormal levels of specific biomarkers, including CD40 ligand (CD154), lymphocyte stimulation, and T or B cell dysfunction. Of 17 screened patients, 14 completed the trial and received IVIG treatment (1 g/kg dose) for ten 21-day treatment cycles. The primary endpoint was disease improvement assessed using standardized cognitive and behavioral tests (Children’s Communication Checklist [CCC-2], Social Responsiveness Scale [SRS], Aberrant Behavior Checklist [ABC], Clinical Global Impressions-Severity [CGI-S] and -Improvement [CGI-I], Autism Diagnostic Observation Schedule [ADOS], and Peabody Picture Vocabulary Test [PPVT]). Secondary endpoints included experimental biomarkers such as CD154, toll-like receptor-4, memory B cells, FOXP3, and lymphocyte stimulation. Significant improvements from baseline to study endpoint were observed in several subscales of the CCC-2, SRS, CGI-I, CGI-S, and ADOS, including Associated Maladaptive Behaviors (p ≤ .043), Reciprocal Social Interaction (p = .015), Communication (p < .001), and Stereotyped Behaviors and Repetitive Interests (p ≤ .013). Statistically significant reductions were also seen in numerous secondary outcomes of immunological biomarkers indicative of neuroinflammation. IVIG was well tolerated; no subjects withdrew due to an adverse event, and clinical data showed no evidence of thromboembolic events.

Biography

Dr. Isaac Melamed is currently a clinician in private practice in the metro Denver area of Colorado. Previously, he was in academia in the US, Canada and Israel. His focus is the interaction between the immune and nervous system – neuroimmune connection. He has published over 150 papers, presenting and lecturing around the world. He also founded an independent clinical research facility, IMMUNOe Research Center, and has been a principle investigator on over 250 clinical trials. His major areas of interest are: Cross-talk between the nervous and immune system, The role of the immune system in neuro-inflammatory diseases, Cytoskeletal signaling
Effect of Neurogenic Compound NSI-189 on Indices of Cognition in 2 Mouse Models of Alzheimer’s Disease.

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Abstract

Background: NSI-189, a benzylpiperizine-aminopyridine, is a proprietary, orally active, new chemical entity that stimulates neurogenesis, synaptogenesis and increased hippocampal volume in mice. It has shown significant antidepressant and pro-cognitive effects in patients with major depressive disorder in a recent Phase II clinical trial. It ameliorated cognitive impairment in a rat model of irradiation-induced brain injury and prevented hippocampal volume decrease in diabetic mice.

Methods: We used two distinct mouse models of AD - 5XFAD and TAPP mice. 5XFAD mice express mutated APP and mutated PSEN1 with consequently high cerebral Ab42 levels and develop cognitive impairments at 4-5 months of age. The TAPP mouse model combines the major hallmarks of AD with formation of both plaques and tangles and these mice develop cognitive deficits by 5 months of age. After confirmation of cognitive impairment at 15-19 weeks of age, mice were treated orally for 12 weeks with NSI-189 at 30 mg/kg. After 6 and 12 weeks of treatment, learning and memory tests (Barnes maze and Object recognition tests) were performed along with repeated testing on the rotarod for assessing motor learning.

Results: Learning disabilities were significantly ameliorated by 12 weeks of oral administration of NSI-189 in both 5XFAD and TAPP mice. The 12-week treatment with NSI-189 improved short-term memory of 5xFAD and TAPP mice beyond the recognition capacity of control mice in the novel object recognition test. Long-term (6 weeks) memory loss was also ameliorated by the 12-week treatment with NSI-189 in TAPP mice. Using the repeated rotarod test, motor performance as well as the motor learning ability of NS-189-treated 5xFAD and TAPP mice were significantly improved to a level above control mice values.

Conclusions: Daily treatment with NSI-189 significantly reversed learning and memory deficits that were established in the 5XFAD and TAPP mouse models of AD.

Arts Integration Improves Learning Outcomes

Mariale Hardiman and Deborah Carran
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Abstract

Strong correlational evidence suggests that exposure to the arts improves a host of positive outcomes for students at all levels of schooling. Moreover, as a growing number of studies suggest that integrating the arts into pedagogical approaches in non-arts subjects enhances learning, few empirical studies have examined the direct effect of an arts-integrated curriculum on students’ retention of non-arts academic content. This presentation will provide preliminary evidence of the causal effects of arts-integrated instruction on memory of science content. Our research team at Johns Hopkins University hypothesized that embedding arts-based activities into conventionally taught lessons would produce learning outcomes as good as or better than traditional instruction. The presentation will describe the results of randomized control trials that measured retention of science content using arts-integrated units and matched units employing convention science instruction. Findings provide causal connections between arts-integrated instruction and better memory for academic content for students who struggle with learning in conventional ways. Our findings also raised questions about whether learning through the arts transfers residual benefits. We found that students who experienced arts-integrated instructional units may have applied arts-based learning strategies on their own even when subsequently taught through conventional methods. We will discuss opportunities for research that examines how the arts may affect long-term learning and potentially creative thinking and problem-solving. The power of the arts to offer rich and diverse ways to enhance instruction and improve learning should be an important focus for future research.
area of significant importance to researchers and to those engaged in educational practice and policy.

Biography

Mariale Hardiman, EdD is a professor at the Johns Hopkins University School of Education. As the Director of the Neuro-Education Initiative at the School, she created academic programs at the doctoral and master's degree level in Mind, Brain, and Teaching. Hardiman's research focuses on the relationship of arts integration and memory and the effects of knowledge of the learning sciences on teacher practices.

Deborah Carran, PhD is a professor at the Johns Hopkins University School of Education, serving as the specialist in research methodology. Dr. Carran teaches doctoral level courses focused on research design, methodology, statistical analysis, and evaluation.

Gut Microbiota and Its Dysbiosis – The Cinderella of Neurological Disorders

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Abstract

Gut microbiota (GM), an organ within an organ, is a complex entity that appears to modulate both local and systemic immune responses. Any imbalance in its composition will alter these immune modulated reactions. Therefore, one can deduce that dysbiosis may contribute to the appearance of several human disorders. Actually, medical literature identifies GM and its dysbiosis as culprits in a wide range of conditions, from gastrointestinal diseases to systemic ones, including metabolic, allergic, autoimmune and tumoral disorders.

The authors intend to synthetize the interactions between GM and the central nervous system on one hand and GM and the human immune system on the other hand. All in order to highlight the possible implications of GM and dysbiosis in the pathogeny of several neurological diseases.

GM and central nervous system appear to interact in a bidirectional way using the gut-brain axis as an anatomical support. The enteric nervous system, influenced by the central nervous system controls gut motility and homeostasis and, therefore will indirectly dictate GM composition. Meanwhile, GM modulates the enteric nervous system through the production of neurotransmitters and neuromodulators and also by genetical interference. Overall, GM appears to influence nociceptive responses, depression, stress responsiveness, anxiety and social interaction.

Throughout the medical literature, several links were found between dysbiosis and several neurological disorders both autoimmune and non-autoimmune.

These cause-effect relations open opportunities regarding potential new treatment measures, including fecal microbiota transplantation in a widely variety of neurologic and psychiatric disorders such as Parkinson's disease, fatigue, multiple sclerosis and autism.

Biography

Croitoru Cristina-Georgiana Was born in June 1989. In 2014 she graduated forth in her year from Faculty of Medicine, University of Medicine and Pharmacy “Grigore T. Popa”, Iasi, Romania. During 2014-2016 she attended the classes of “Management of Health services in medical and pharmaceutical domain” Master at the same university. From 2017 until present she is a PhD student in the Immunology-Immunopathology department, at the same university, with a PhD study regarding "Considerations upon HLA genotype and autoantibodies profile in Myasthenia Gravis". From January 2019 she is a Specialist in Neurology and works at "Professor Doctor Nicolae Oblu" Emergency Clinical Hospital, Iasi.
Oral Presentations

PRISM Clinical Study: EEG Biomarker Group Analysis

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Abstract

Introduction: In the Psychiatric Ratings using Intermediate Stratified Markers (PRISM) project1, EEG is one of the tools selected to delineate the neurobiology and associated phenotypes that may underlie Social Withdrawal in Alzheimer and Schizophrenic patient populations. Different EEG paradigms have been selected on the basis of their test-retest reliability, capacity to discriminate between populations and acceptability as recognized biomarkers involving sensory processing. Here we present the results of the PRISM EEG analysis.

Method: Six EEG paradigms are used for assessments: resting state, auditory mismatch negativity (MMN), auditory and visual oddball paradigms (P300), facial emotion processing (FEP), ERPs and auditory steady-state response (ASSR). Age-matched healthy controls were split into two subgroups: young (YC), and aged (AC) controls (up to, and older than 50 years old), to eliminate the age effect when comparing with Schizophrenia (SZ) or Alzheimer (AD) patients. Effect of age was also analyzed as YC vs AC.

Results: Significant inter-group differences in endpoint values, their topographic maps distribution, and grand average ERP shapes, are observed. In both auditory and visual P300, there is a notable peak value difference in SZ vs YC, and age effect is clearly noted in YC vs AC. For auditory P300, in AD vs AC, a difference in the peak location and scalp distributions is observed.

Similarly, a notable difference is observed in the MMN peak values in SZ vs YC, and YC vs AC.

In ASSR, we observe a strong phase locking factor difference in SZ vs YC and YC vs AC and a reduced difference in AD vs AC. Frontal evoked power is noticed only in SC and induced power in AD.

Antidepressants Medication for Depression, Apathy, and Gait Instability in Parkinson's Disease: A Multicenter Randomized Study in Japan

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Abstract

Objective: Depression, apathy, and gait freezing are cardinal symptoms in patients with Parkinson's disease (PD). In general, selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) are used for treating the psychiatric symptoms of PD. To compare the efficacy of an SNRI (duloxetine) with SSRIs (paroxetine, escitalopram) in improving depressive symptoms and apathy and freezing of gait, we conducted the first prospective randomized study in patients with PD.

Methods: In this prospective, multicenter, open-label, randomized study, PD patients with a Quick Inventory of Depressive

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Symptomatology-Japanese (QIDS-J) score of 6 were randomly assigned to receive an SSRI (27 enrolled, 25 analyzed) or duloxetine (28 enrolled, 27 analyzed) and were assessed at 6 and 10 weeks.

**Results:** The mean change (SD) in the QIDS-J [SSRI: -2.4 (3.6), p=0.015; SNRI: -2.3 (3.9), p=0.029] and FOG-Questionnaire [SSRI: -2.9 (4.2), p=0.012; SNRI: -3.4 (4.7), p=0.010] scores (from baseline) at 10 weeks was statistically significant, while the mean change in the Apathy Scale scores was not [SSRI: -2.7 (5.4), p= 0.054; SNRI: -1.5 (3.7), p=0.109]. No significant differences in QIDS-J, FOG-Q and Apathy Scale were observed between the SSRI and SNRI groups. The treatments were well-tolerated; however, gastrointestinal events were more common with SSRIs. Two SNRI-treated patients reported an exacerbation of tremor.

**Conclusion:** SSRIs and SNRIs equally improve the depressive symptoms and FOG in PD patients with mild to severe depressive symptoms. However, their effectiveness in treating apathy remains to be elucidated.

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**The Blood Brain Barrier Disruption: The Plasma Kallikrein-Kinin System Contributes to Peripheral Inflammation in Temporal Lobe Epilepsy**


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**Abstract**

Temporal lobe epilepsy (TLE), a disease characterized by refractory seizures, induces blood brain barrier (BBB) disruption by unclear mechanism. Among all inflammatory markers in TLE, the plasma kallikrein-kinin system (KKS) has received special attention. The aim of this work was to evaluate the KKS activation in patients with TLE, as it relates to maintenance of the BBB. Hippocampal sclerotic tissues were used in immunostaining for white blood cells. In plasma and serum were investigated neutrophil/lymphocyte ratio, levels of C-reactive protein (CRP), C1-inhibitor, plasma kallikrein (PKal) and cathepsin B (CatB) activity, high-molecular-weight kininogen (H-kininogen) cleavage, and activation of plasma prekallikrein (PK). Infiltration of white blood cells in the sclerotic hippocampus, and a significant increase in the neutrophil/lymphocyte ratio in the blood of patients (TLE 3.72 ± 0.58; control 1.56 ± 0.12) were observed. High levels of CRP (TLE 1.4 ± 0.3 µg/mL; control 0.53 ± 0.07 µg/mL), PKal (TLE 5.4 ± 0.4 U/mL; control 1.6 ± 0.1 U/mL) and CatB (TLE 4.9 ± 0.4 U/mL; control 1.7 ± 0.1) were evident in the serum of patients. A strong linear correlation was observed between active CatB and PKal in the serum of patients (TLE r = 0.88). The H-kininogen fragments (TLE 1,270 ± 143 D.U.; control 424 ± 32 D.U.), free PKal (TLE 48 ± 5%; control 27 ± 4%) and low levels of C1-inhibitor in the serum of patients (TLE 188 ± 12 µg/mL; control 249 ± 8 µg/mL) were observed. Our data demonstrated the KKS activation in patients with TLE.

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**Deletion of FOXG1 Transcriptional Enhancers is Associated with Rett-Like Syndrome**

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**Abstract**

Gene regulatory elements such as enhancers dynamically regulate gene expression in a tissue-specific manner. However, the transcriptional regulatory elements during human inhibitory interneuron differentiation and their role in neurodevelopmental disorders are unknown. Here, we generated gene regulatory element maps of human inhibitory-like interneurons derived from embryonic stem cells (H9-ESC), permitting large-scale annotation of previously uncharacterized regulatory elements relevant to inhibitory interneuron differentiation. Our analyses identify neuronal progenitor enhancers that likely regulate the expression of transcription factors that are essential for interneuron differentiation. Haploinsufficiency of FOXG1, a transcription repressor that is specifically expressed in interneuron progenitors, is associated with Rett-like syndrome. Using in vivo enhancer assay, we identified 8 transcriptional enhancers in the FOXG1 locus with activity patterns that resembled FOXG1 expression. Using CRISPR/Cas9 genome editing, we deleted two FOXG1 enhancers that reduced FOXG1 expression in human cells and altered cell proliferation. Furthermore, a microdeletion proximal to FOXG1 encompassing these neuronal FOXG1 enhancers was found in patient with Rett-like syndrome, supporting the role of FOXG1 enhancers in this syndrome. Our study provides a framework for understanding the impact of non-coding regulatory elements during inhibitory interneuron differentiation, and highlights novel mechanisms underlying neurodevelopmental disorders.
The Current and Emerging Therapeutic Approaches in Drug-Resistant Epilepsy Management

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Abstract

Epilepsy is a neurologic disorder consisting of recurrent spontaneous seizures. Antiepileptic drugs administration is the most commonly used therapeutic strategy in the management of epilepsy. However, 20–30% of epilepsy patients have seizure episodes that are not controlled by these medicines (drug-resistant epilepsy). The management of drug-resistant epilepsy, especially in the children, is challenging and can cause economic and social problems, and lower the patients’ quality of life, cognition, and mood. Several therapeutic approaches for drug-resistant epilepsy are available including surgical methods, neurostimulation treatments, and diet therapies which lead to diminishing the epileptic seizures. An increasing number of novel and potential therapeutic approaches such as gene therapy, gene editing, cell therapy, exosome therapy, and molecular network targeting have also been explored. The present study is aimed to review these current and emerging therapeutic approaches for drug-resistant epilepsy.

Biography

Sina Raeisi has finished his Ph.D. in Clinical Biochemistry at Tabriz University of Medical Sciences, Tabriz, Iran. He is interested in Neuroscience field. He has been working as an Assistant Professor in Pediatric Health Research Center of Tabriz University of Medical Sciences since 2017. They are mainly working on the signal transduction pathways, oxidative stress, inflammation, proteins exhibiting mutations, and their association with pediatric neurological diseases to understand the underlying mechanisms and find the therapeutic approaches.

Dynamics of the function of the Shoulder Joint in Patients with Hemiparesis During the Acute Stage of Hemispheric Stroke

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Abstract

Upper limb dysfunction after Cerebral stroke lead to a persistent loss of working ability, alter the quality of life and affect the psychological and emotional state of patients and their loved ones. In our study, we evaluated how modified biomechanical and EMG parameters at shoulder joint at hemiparesis in the acute period and functional dynamics of the shoulder joint during a treatment at acute period and which type of treatment is more effective. Control group included 25 healthy persons. The first group of 25 patients with hemiparesis during the acute stage of first-ever hemispheric stroke: a group receiving conventional therapy (CT group). The second group of 25 the same type of patients: a group receiving along with CT the biofeedback (BF) training (CT&BF group). The study of patients was conducted before and after the individual set of rehabilitation measures: on the 3-5th day and after the course completion on the 21st day. Each of the participants passed a standard clinical examination and biomechanics investigation of kinematics of shoulders joints and trunk movement, and of EMG of girdle shoulders muscles. The results of the studies by the clinical scales did not show statistically significant differences in patients group. We noted decrease of all the basic amplitudes of the paretic limb and later EMG maximum activity. As a result of rehabilitation discovered a slight improvement of the paretic limb with somewhat better dynamics in the CT&BF group.

Location of Cerebral Atherosclerosis; Why is there a Difference Between East and West?

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Abstract

Intracranial atherosclerosis (ICAS) is more prevalent in Asian patients whereas extracranial atherosclerosis (ECAS) is more common in the Western counterparts. However, the reasons for this racial difference remain uncertain. We reviewed the literature of cerebral atherosclerosis (ICAS, ECAS or comparison between ICAS and ECAS) and discussed currently available knowledge on this issue.

Although study population, diagnostic modality, and definition of risk factors differ across studies, it seems clear that
hypercholesterolemia is more closely associated with ECAS than ICAS, suggesting that ethnic difference in the prevalence of hypercholesterolemia is one of the reasons for the racial differences. Intracranial arteries contain more abundant antioxidants than extracranial arteries, and may be vulnerable to risk factors that deplete antioxidants such as metabolic syndrome, diabetes mellitus, and perhaps smoking. Due probably to smaller diameter, thinner media and adventitia, and fewer elastic medial fibers than extracranial arteries, intracranial arteries appear to be vulnerable to factors associated with hemodynamic stress, e.g., advanced, salt-retaining hypertension and arterial tortuosity. In addition, non-atherosclerotic arterial diseases such as moyamoya disease and dissection commonly occurring in intracranial arteries in East Asians, may contaminate ICAS cases, which seems to be another reason for the reported predominance of ICAS in Asia. Genes such as RNF 213 or those associated with high salt sensitivity may also explain racial differences in atherosclerosis location.

We conclude that to understand racial differences, further well-designed risk factors and genetic studies should be performed. Additionally, improvements in diagnostic accuracies with more advanced imaging technologies and genetic knowledge should be achieved to differentiate atherosclerotic from non-atherosclerotic intracranial diseases.

**Accuracy of Computed Tomography Perfusion in Diagnosis of Brain Death: A Prospective Cohort Study**

**Marcin Sawicki**, **Joanna Sóleń-Pastuszka**, **Katarzyna Chamier-Ciemnińska**, **Anna Walecka** and **Romuald Bohatyrewicz**

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2 Clinic of Anesthesiology and Intensive Care, Pomeranian Medical University in Szczecin, Poland

**Abstract**

**Background:** This study was designed to determine diagnostic accuracy of computed tomographic perfusion (CTP) compared to computed tomographic angiography (CTA) for the diagnosis of brain death (BD).

**Material and methods:** Whole-brain CTP was performed in patients diagnosed with BD and in patients with devastating brain injury with preserved brainstem reflexes. CTA was derived from CTP datasets. Cerebral blood flow (CBF) and volume (CBV) were calculated in all brain regions. CTP findings were interpreted as confirming diagnosis of BD (positive) when CBF and CBV in all ROIs were below 10 mL/100 g/min and 1.0 mL/100 g, respectively. CTA findings were interpreted using a 4-point system.

**Results:** Fifty brain-dead patients and 5 controls were included. In brain-dead patients, CTP results revealed CBF 0.00–9.98 mL/100 g/min and CBV 0.00–0.99 mL/100 g, and were thus interpreted as positive in all patients. CTA results suggested 7 negative cases, providing 86% sensitivity.

In the non-brain-dead group, CTP results revealed CBF 2.37–37.59 mL/100 g/min and CBV 0.73–2.34 mL/100 g. The difference between values of CBF and CBV in the brain-dead and non-brain-dead groups was statistically significant (p=0.002 for CBF and p=0.001 for CBV). CTP findings in all non-brain-dead patients were interpreted as negative. This resulted in a specificity of 100% (95% CI, 0.31-1.00) for CTP in the diagnosis of BD. In all non-brain-dead patients, CTA revealed preserved intracranial filling and was interpreted as negative. This resulted in a specificity of 100% (95% CI, 0.31-1.00) for CTA in diagnosis of BD.

**Conclusion:** Whole-brain CTP seems to be a highly sensitive and specific method in diagnosis of BD.

**Biography**

Dr. Marcin Sawicki is an Assistance Professor in the Department of Diagnostic Imaging and Interventional Radiology of the Pomeranian Medical University in Szczecin, Poland. Dr. Sawicki's main research interests: diagnostics of brain death and stroke, endovascular treatment of neurovascular diseases. He has published 42 full text papers including 21 original articles. He was also invited invited by the Council of Europe to the group of experts preparing the 7th EDITION OF GUIDE TO THE QUALITY AND SAFETY OF ORGANS FOR TRANSPLANTATION (including chapter: DETERMINATION OF DEATH BY NEUROLOGIC CRITERIA). Dr. Sawicki has presented his work at 70 international and national scientific conferences.

**Different Patterns of Cortical Reorganization During Motor Recovery in Chronic Stroke Patients with Severe Motor Impairment**

Qiurong Yu*, Shuang Zhan**, Limin Sun3, Hewei Wang2, Dazhi Yin1, Yu Wei1, Xuefei Wang1 and Mingxia Fan1

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Abstract

Previous imaging studies have demonstrated brain plasticity following rehabilitation intervention in chronic stroke patients. The purpose of this study is to investigate whether there are different functional recovery patterns in stroke patients with similar severity of motor deficits. 30 severe stroke patients with unilateral subcortical lesions underwent resting-state fMRI before and after 4-week rehabilitation intervention. They were divided into two subgroups according to their functional connectivity density (FCD) between bilateral primary motor cortex (M1): high-FCD group (FCD>0.3, 11 patients) and low-FCD group (FCD<0.3, 19 patients), respectively. 25 healthy controls (HC) were also recruited. Functional connectivity (FC) in the ipsilesional M1 were performed to explore differences among the three groups. Compared with HC, no significant different FC were observed in pre- and post-intervention high-FCD group. However, FC reduced dominantly with the contralesional sensorimotor cortex in the pre-intervention low-FCD group, which recovered slightly after the intervention. Meanwhile, FC increased in the ipsilesional cerebellum and inferior parietal lobule before treatment, but it turned into the ipsilesional inferior frontal gyrus and contralesional cerebellum after treatment. When comparing post- with pre-intervention, only FC increased in the ipsilesional cerebellum of high-FCD group. Moreover, the values of pre-intervention FC with the contralesional occipital lobe were positively correlated with the increment of upper extremity section of FMA scores (FM-UE). All results are shown in Figure 1. It was noted that FC patterns of ipsilesional M1 were distinct different before and after efficient intervention in stroke patients with clinically similar motor severity. This may provide guidance for future more precise and targeted treatments of post-stroke patients.

Author Biography

Qiurong Yu is a Ph. D student from Shanghai Key Laboratory of Magnetic Resonance of East China Normal University supervised by Dr. Mingxia Fan. Her research interests are the application and development new magnetic resonance imaging techniques in neuroscience. In recent years, their research group focused on stroke motor dysfunction research by using fMRI.

Neuro-psychological and Motor Effects of Rehabilitation In Medical Pools, for Patients With Severe Brain Injuries

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Abstract

With the present study, we present the preliminary data of 16 clinical cases of patients with GCA, attending the Adelphi Day Center, ASL ROMA 1, Osp. Santa Maria della Pietà, Rome, included in the motor rehabilitation program in the medical pool. The inclusion criteria included male subjects, aged between 40 and 50 years, with traumatic brain injury, with LCF> 7 in individual daily treatment, for a total of 10 months. Before entering into the water, (TO) each patient had an interview with the psychologist to assess expectations and fears related to the water element, to his own body and to the manipulation performed by nurses staff during the physical preparation. All Patients were subjected to administration of tests for the evaluation of anxiety (SAS, ASI), depression (BDI), quality of life (SF36), body image (semi-structured interview) and a neuropsychological evaluation, with ENB. DRS, GOE-S and ASHORT scales were administered for the evaluation of motor effects. The first accesses, having as main objective the familiarization with the water element, were based, mainly, on relaxation exercises and assisted floating. In the following steps, elements of increasing difficulty are inserted in a programmatic way, such as: head control, trunk and upper and lower limbs control; at the end, we proposed walking and swimming exercises. At the end of the rehabilitation course in the medical pool, the patients are re-administered the evaluation tests of the components investigated at the entrance. (T8) From the semi-structured interview, there emerges a greater awareness of one's body and greater tolerance to frustration in being physically manipulated and in the individual perception of pain.

The ENB documents an increase in the values of all 4 attentions. Note the implementation of movement quality (speed of execution, and amplitude). The element water, in our experience, despite the poor dry reproducibility, appears fundamental in the construction of a therapeutic path, which develops in a continuum that continues in the gym and in daily life and manifests both positive effects on the orientation of the tone of the mood and on the QoL, as the “water” fluid, which cushions and protects from possible falls, guarantees the patient the possibility of moving in greater safety, favoring independence and greater acceptance of his status.

Depression is an Independent Determinant of Life Satisfaction Early After Stroke

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Abstract

Objective: Life satisfaction is reduced in stroke patients. However, as a rule, rehabilitation goals are not aimed at life satisfaction, but at activities and participation. In order to optimize life satisfaction in stroke patients, rehabilitation should take into account the determinants of life satisfaction. The aim of this study was therefore to determine what factors are independent determinants of life satisfaction in a large group of patients early after stroke.

Methods: Stroke-surviving patients were examined by a specialized nurse 6 weeks after discharge from hospital or rehabilitation setting. A standardized history and several screening lists, including the Lisat-9, were completed. Step-wise regression was used to identify independent determinants of life satisfaction.

Results: A total of 284 stroke-surviving patients were included in the study. Of these, 117 answered all of the Lisat-9 questions. Most patients (66.5%) rated their life as a whole as “satisfying” or “very satisfying”. More depressive symptoms were independently associated with lower life satisfaction (p < 0.001).

Conclusion: Most stroke-surviving patients are satisfied with their life early after a stroke. The score on the Hospital Anxiety and Depression Scale depression items is independently associated with life satisfaction. Physicians should therefore pay close attention to the mood of these patients.

Neural Progenitor Cell-Derived Extracellular Vesicles – A Pre-Clinical Evaluation for Stroke Treatment

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Abstract

Stem cells such as mesenchymal stem cells (MSCs) and neural progenitor cells (NPCs) increase neuroregeneration and neurological recovery after stroke. However, grafted cells are not integrated into residing neural networks, but mediate these effects by secretion of extracellular vesicles (EVs). The latter are a heterogeneous group of vesicles that are secreted by eukaryotic cells, containing different proteins and non-coding RNAs. Nevertheless, current data is exclusively based on the application of MSC-derived EVs under stroke conditions. We therefore evaluated the therapeutic potential of NPC-derived EVs under conditions of in vitro hypoxia and in vivo cerebral ischemia. As such, EVs were applied to cerebral organoids that have been exposed to hypoxia followed by reoxygenation
under standard cell culture conditions. EV treatment under these conditions significantly reduced cell death rates of organoids in comparison to control organoids. To investigate the effects of NPC-EVs in vivo, EVs were systemically delivered to mice on days 1, 3, and 5 post-stroke in mice that were allowed to survive for 84 days. EVs significantly reduced post-stroke brain injury on day 84, which was associated with a better neurological outcome in the corner turn test and tight rope test. In this context, application of EVs under in vivo stroke settings significantly stimulated post-stroke neuroregeneration and axonal plasticity. The present study therefore for the first time provides clinically relevant evidence that NPC-derived EVs are equal to MSC-derived EVs in terms of their therapeutic potential under experimental stroke settings, warranting rapid proof-of-concept studies of NPC-derived EVs in stroke patients.

Good Outcome in a Patient with Massive Pontine Hemorrhage

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Abstract

Massive pontine hemorrhage with comatose condition has a poor prognosis and bad outcome despite adequate surgical treatment. However, this case report gives a different result. Providing adequate prophylactic treatment to prevent secondary brain injury resulted in a very good recovery at the 6-month follow-up. A 42-year-old man with a history of heavy smoking and poorly controlled blood pressure (BP) developed acute loss of consciousness. He was then brought to the emergency room (ER) in 30 min. At the ER, his Glasgow coma scale score was E1M2V1 and the BP was high. An emergency computed tomography (CT) scan of the brain showed massive hematoma in the pons with intraventricular extension. He was admitted to the intensive care unit with close monitoring of both vital signs and neurosigns. External ventricular drainage was inserted to control intracranial pressure and then removed in only 5 days after adequate control. The patient returned to a good recovery status in 6 months with a modified Rankin scale score of 2 and the CT brain scan showed a small cavity-like lesion at the hemorrhage area. Massive hemorrhage and low consciousness may not truly indicate a poor prognosis in patients with pontine hematoma. Medical and surgical treatments are still needed to control intracranial pressure for prophylaxis of secondary brain injury. Restoration of neuronal functions was achieved after resolution of the hematoma.

Biography

Somkrit Sripontan is a head of Neurological Surgery division in Mahasarakham General hospital, Thailand, who has many experiences in managements of traumatic brain injury and stroke cases. He wants to change view of treatments in Pontine hemorrhage to full support and wait for patient recovery.

RORA Modulates Semaphorin 3e Transcription and Neurovascular Interaction in Pathological Retinal Angiogenesis

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5Department of Immunology and Microbiology, The Scripps Research Institute, Jupiter, Florida, USA

Abstract

Pathological proliferation of retinal blood vessels commonly causes vision impairment in proliferative retinopathies, including retinopathy of prematurity. Dysregulated crosstalk between the vasculature and retinal neurons is increasingly recognized as a major factor contributing to the pathogenesis of vascular diseases. Class 3 Semaphorins (SEMA3s), a group of neuron-secreted axonal and vascular guidance factors, suppress pathological vascular growth in retinopathy. However, the upstream transcriptional regulators that mediate the function of SEMA3s in vascular growth are poorly understood. Here we showed that retinoic acid receptor–related orphan receptor a (RORa), a nuclear receptor and transcription factor, is a novel transcriptional regulator of SEMA3Emediated neurovascular coupling in a mouse model of oxygen-induced proliferative retinopathy. We found that genetic deficiency of RORa...
substantially induced Sema3e expression in retinopathy. Both RORα and SEMA3E were expressed in retinal ganglion cells. RORα directly bound to a specific ROR response element on the promoter of Sema3e and negatively regulated Sema3e promoter– driven luciferase expression. Suppression of Sema3e using adeno-associated virus 2 carrying short hairpin RNA targeting Sema3e promoted disoriented pathological neovascularization and partially abolished the inhibitory vascular effects of RORα deficiency in retinopathy. Our findings suggest that RORα is a novel transcriptional regulator of SEMA3E-mediated neurovascular coupling in pathological retinal angiogenesis.

Biography
Ye Sun, MD, PhD, Assistant Professor of Ophthalmology at Harvard Medical School. Dr. Sun's research interests focus on the roles of neurovascular interaction and neuroinflammation in the development of vascular eye disorders including neovascular AMD, retinopathy of prematurity and diabetic retinopathy and tumorigenesis using mouse models, and develop effective ways to treat or prevent vision loss and cancer. Her current research projects include: 1) the mechanisms of neurovascular interaction in controlling retinal neovascularization; 2) SOCS3 mediates retinal neovascularization and neuroinflammation; 3) c-Fos controls neovascularization and inflammation.

Risk of Stroke After Exacerbation of Ischemic Heart Disease: Data of 3-Years Follow-Up: Data From Oracle I And Oracle II Studies
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Abstract
Aim of the study was to analyze the possible association of clinical and genetic factors with the development of strokes in patients after acute coronary syndrome (ACS). We analyzed the data from two prospective observational trials - 1193 pts with ACS were included in 2004-2007 and 952 pts - in 2014-2018. In ORACLE I study We included 1193 patients with ACS (63.2% men, mean age 61.1±0.34 years). Inclusion into the study was performed in 2004-2007. 1652 patients with ACS were included in ORACLE II study (mean age 64.61 ± 12.672 years, 1029 (62.3%) - men). Inclusion into the study was performed in 2014-2017 years. Duration of the follow-up – 2 years. In the first study we tested SNP in CRP, IL-6, IL-10, TNF, LTA, ApoB, KIF6 and PROC genes, in the second study – TNF and ANXA2 genes.

Results: There were 37 strokes during follow-up period in ORACLE I study and 42 stokes in ORACLE II. In the first study only carriage of А allele of G(-1082)A polymorphism of IL-10 gene was associated with risk of stroke: OR 1,54 [1,02-2,65], p=0,043. Carriage of А allele of IL-10 gene, BP level, history of MI, recurrent severe ischemia and atrial fibrillation during index hospitalization and absent of antithrombotic therapy were independently associated with stroke risk. In ORACLE II study we do not found the association between stroke risk and genetic polymorphism. BP and HDL levels, GFR, PCI, heart failure, atrial fibrillation and anticoagulant treatment were associated with the risk of ischemic stroke.

Biography
Minushkina Larisa O MD, Ph.D., Professor of the Therapy, Cardiology and Functional Diagnostics Department of Central State Medical Academy of the Presidential Affairs Office, Moscow, Russia. Secretary of the section of genetic and pharmacogenetic of the Russian Cardiology Society

NIHSS Discrepancy and Reliability in Stroke Triage
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Abstract
The National Institute of Health Stroke Scale (NIHSS) is the standard metric in both clinical practice and stroke research used to
establish a baseline in patients suffering from an acute ischemic stroke (AIS). The initial score severity during triage has direct impact in guiding the appropriate treatment. In this study, we sought to examine the reliability of the NIHSS when scored by neurology clinicians versus emergency department (ED) clinicians. NIHSS scores were obtained from 1092 patients being evaluated for AIS at Houston Methodist Hospital from 05/2016 – 04/2018. The initial (baseline) NIHSS score was obtained from the clinical documentation of the neurology and ED providers. Patients were only included if the treatment status was the same (pre-treatment, post-treatment, or no treatment) and if there was no significant time delay between the recorded scores (<1 hour). 142 patients were ultimately included for analysis. The distribution of the NIHSS score difference (neurology score – ED score) had a mean of 0.827 and standard deviation of 2.901. The intraclass correlation coefficient for total score was 0.91 (95% CI, 0.87 - 0.94). Reliability was excellent between the groups with no significant difference between the NIHSS scores. There were 7 outliers (4.93%) with >5 difference in the NIHSS scores. These were individually examined, and most were found to result from improper NIHSS scoring in the ED (incongruity between the ED clinical exam findings and reported NIHSS score). In hospitals and EDs where a stroke trained neurology clinician is not available, the reliability of the triage NIHSS score from the ED provider is paramount in establishing the patient baseline and guiding treatment.

Biography

Dr. John Volpi is the Co-Director of the Houston Methodist Hospital Stroke Center. He has participated in over 100 research studies as an investigator, and is currently a lead investigator (PI, co-PI, or Neurology PI) in 20 ongoing research studies in stroke, cardiovascular disease, and neurological rehabilitation, as well as a national PI for a post marketing study of the Gore Septal Occluder for PFO closure and stroke risk reduction. He is a recognized expert in cryptogenic stroke diagnosis and management and serves as a reviewer for the Neurology journal, and has been an invited reviewer for NIH grants.

Apelin Induces the Proliferation, Migration and Expression of Cytoskeleton and Tight Junction Proteins in Human RPE cells via PI-3K/Akt and MAPK/Erk Signaling Pathways

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Abstract

Diabetic retinopathy is major cause of vision loss during working age. Breakdown of blood-retinal barrier is an early event in pathogenesis of DR. RPE is the major part of outer BRB. Apelin, an endogenous ligand of APJ, mediates angiogenesis. Our previous study showed that apelin induced proliferation, migration, and collagen I mRNA expression in human RPE cells via PI-3K/Akt and MAPK/Erk signaling pathways. Now we investigate the connection between apelin and RPE in vascular permeability of diabetic retinopathy and its working mechanism. Our study showed that apelin promotes the proliferation, migration and expression of cytoskeleton and tight junction proteins in human RPE cells using MTS and transwell chamber assay. Apelin also activated the expression of PI-3K/Akt and MAPK/Erk signaling pathways proteins, such as PLCγ1, p38, Akt and Erk phosphorylation in RPE cells using laser scanning confocal detection, PCR and western blot. Pretreatment with the inhibitor of apelin receptor APJ, F13A, abolished the apelin-induced activations of the proliferation, migration and expression of cytoskeleton, tight junction and PI-3K/Akt and MAPK/Erk signaling pathways proteins in human RPE cells. It suggested that apelin as a promoter in retinal vascular permeability during early stage of DR, provides further evidence for neurovascular crosstalk in pathogenesis of DR, which may offer a new target in early prevention and treatment of DR.

Secondary Prophylactic Treatment and Long-Term Prognosis after TIA and Different Subtypes of stroke.
A 25-year Follow-up Hospital-Based Observational Study

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Running head: Secondary prophylactic treatment after TIA/stroke

Abstract

Objectives: To assess long-term prognosis after transient ischaemic attack (TIA)/subtypes of stroke relative to secondary prophylactic treatment(s) given. Materials and Methods: Retro/prospective follow-up of patients hospitalized in the Stroke Unit or in the Department of Neurology, Linköping, in 1986 and followed up to Feb. 2011. Results: A total of 288 men were followed up for 2254 yrs. (mean 7.8 yrs.) and 261 women for 1984 yrs. (mean 7.6 yrs.). In men, the distribution to anticoagulants (AC) (warfarin treatment) was 18%, antplatelet therapy (APT) usually ASA 75 mg/day 54%, untreated 27%, unknown 2%. In women, the distribution to AC was 15%, APT 60%, untreated 23%, unknown 2%, respectively. Mortality rates at 1 year, 10 years, and 25 years for men were 21%, 67%, and
93%, respectively, versus the rates in women of 24%, 71%, and 90%, respectively. Survival curves showed markedly increased risk of death compared to the normal population. AC treatment was more favourable for men regarding the annual risk of stroke, compared with APT (9.4% vs 9.8%), as well as the risks of MI, (5.6% vs 6.7%), and death (8.1% vs 10.3%), compared to women for stroke (11.6% vs. 8.8%) and MI (5.3% vs. 3.7%) but not for death (8.3% vs. 8.4%). The risk of fatal bleeding was 0.86% annually on AC compared to 0.17% on APT. According to Cox regression analysis included patients with TIA/ischaemic stroke, first-line treatment had beneficial effects on survival: AC OR 0.67 (0.5-0.9), APT 0.67(0.52-0.88) versus untreated.

Conclusions: Patients with a history of TIA/stroke had a higher mortality rate versus controls, providing support for both primary and secondary prophylaxis regarding vascular risk factors for death. This study also provided support for secondary prophylactic treatment with either AC or ASA (75 mg once daily) to reduce the vascular risk of death unless there are contraindications.

Social Determinants and Cardiovascular Disease Mortality in Panama, 2012-2016

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Abstract

Background Methods: The geographic and time variation of social determinants of health (SDH) and cardiovascular disease (CVD) mortality in Panama were studied. We also identified which of the SDH has the strongest correlation with a socioeconomic-index (SEI). Data was obtained from the National Mortality Register and socioeconomic variables derived from the National Household Survey (NHS). The ICD 10th revision codes I20-I25 and I60-I69 were used for ischemic heart disease (IHD) and stroke, respectively. Standardized age-adjusted mortality rates were calculated by direct method. Mortality rates and socioeconomic variables were evaluated together in a panel data model. A SEI was developed from factorial analysis by principal components with a polychoric correlation matrix. Provinces and regions were categorized in tertiles according to median value of the SEI score.

Results: The NHS evaluated an average of 15,919 households per year. The mean of age throughout the study period was 41 years. The average monthly income increased, from US$ (SD) 331.94 (5.38) in 2012, to 406.24 (5.81) in 2016, whereas the social security health coverage remained in a range of 57-58%. Significant geographical and temporal variations in social determinants and mortality rates were observed throughout the country. Colon, categorized in the middle tertile according to the SEI, presented higher IHD mortality rates. Darién (in the lowest SEI tertile) Colón and Herrera had higher stroke mortality rates. The SEI categorized indigenous territories in the lowest tertile. Total years of education was the strongest correlated variable with the SEI.

Conclusion: We observed geographical and temporal disparities in SDH and CVD mortality rates. Further epidemiological studies are warranted in the provinces of Colón, Darien, Herrera and Los Santos to explore in-depth the higher CVD mortality rates observed in these provinces.

Sex Differences in Cerebrovascular Disease

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Abstract

Despite several advancements in stroke care, disparities continue to exist with regards to gender differences in cerebrovascular disease. These gender differences are due to a combination of several factors, many of which are unique to the female sex. Some of these unique factors, such as pregnancy and menopause, are related to hormonal changes seen throughout the female life cycle. Hormonal fluctuations, which impact the protective effects of the female sex hormones, can be induced by the use of hormonal contraception. Other risk factors, although present in both sexes, have a higher prevalence in elderly females, such as atrial fibrillation leading to cardioembolic strokes. Similarly, differences in pre-morbid modified Rankin Scale has an impact on the differences in stroke outcome between the two sexes. Clinical research aimed towards highlighting potential causes of these disparities has shown important differences in the calibers of blood vessels in the cerebral circulation between the two genders, whereas basic science research has shown differences in circulating endothelial progenitor cells pools between males and females, with higher levels being
more protective. With the increasing awareness of these gender differences, future research is being geared towards gender specific modes of therapy, focusing in at the molecular level, as well as the individual patient.

Biography

Dr. Aurangzeb Memon was born and raised in Toronto, Canada before relocating to Pakistan at the age of 17. After completing his pre-medical and medical training in Pakistan, he pursued a neurology residency in Buffalo, New York, which helped foster a keen interest in vascular neurology. He underwent subspecialty fellowship training in vascular neurology in Houston, Texas, where he worked under the mentorship of Dr. Louise McCullough. He is board certified in both neurology and vascular neurology by the American Board of Psychiatry and Neurology. Dr. Memon currently resides in Alabama seeing patients in a neurologically underserved community.

Is There an Influence of Circadian Variation in Ischemic Stroke Occurrence on the Rehabilitation Outcome?

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Abstract

Introduction: Data concerning the chronobiology of ischemic stroke describes a circadian variation in ischemic stroke onset with the highest incidence in the morning according to most literature reports. The influence of these findings on the evolution of the severity of the neurological picture, disability and cognitive impairment is little studied.

Materials and Method: Our work presents a retrospective study including 1083 patients the purpose of which was to determinate the temporal pattern of ischemic stroke occurrence variation in Cluj-Napoca area and a cohort study including 63 patients with ischemic stroke admitted to the Neurology Departments of the Rehabilitation Hospital in Cluj-Napoca, followed up for 2 years and evaluated concerning the severity of the clinical picture, disability degree and cognitive status.

Results and conclusions: Our study confirms the incidence pattern of ischemic stroke with a morning peak. Patients with stroke onset in the nocturnal interval have a less favorable neurological, cognitive and functional evolution during the second year after ischemic stroke.

Key words: ischemic stroke occurrence, circadian variation, disability, cognitive decline, neurorehabilitation.

Poster Presentations

Ratio Aβ 1-42: P-Tau: A Possible Diagnostic Tools in Differentiating Dementias.

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Abstract

Background: Patients with Alzheimer’s disease (AD) presents a typical biochemical profile of biomarker: low concentration of β amyloid 1-42 (Aβ1-42), high concentration of total Tau (t-Tau) and phosphorylated Tau (p-Tau). Several neurodegenerative disease may overlap with AD, both in regards to clinical symptoms and neuropathology. AD pathophysiology can be identified using biomarkers. It has been hypothesized that subjects with dementia due to AD showed low levels of Aβ1-42 combined with the highest levels of t-Tau and p-Tau; moreover it has been hypothesized that the ratio Aβ1-42/p-Tau further help in discriminating Alzheimer’s disease from other diagnoses. The aim of this work is to investigate if it could be a sensitive index able to discriminate MCI due to neurodegenerative factors (MCId) from MCI due to vascular factors (MCIV).

Methods: 231 patients meeting the NIA-AA and NINDS-AIREN criteria were diagnosed as follow: AD in 120 patients, FTD in 23 patients, LBD in 17 patients, VAD in 9 patients, 24 patients had the diagnosis of MCId, 38 MCIV. The comparison between the ratio of Aβ1-42/p-Tau among groups was done using t-test for independent samples. A p value < 0.05 represent statistical significance. R-studio software was used for ROC curve analysis.
Results: Aβ1-42/p-Tau was significantly lower in AD and MCId respect to all the other groups and the difference was also statistically significant between MCId and MCIV.

Conclusion: Aβ1-42/p-Tau can be implemented in the clinical routine for differential diagnosis between AD and other dementias and to distinguish underlying pathology such as neurodegeneration or vascular disease.

Molecular Basis of Preventive Effects of Coffee on Neurodegenerative Diseases

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Abstract

Recent epidemiological studies have showed that daily coffee consumption has been associated with a lower risk of several neurodegenerative diseases including Alzheimer's disease and Parkinson's disease. Therefore, we investigated the molecular mechanism underlying the preventive effects of coffee on the neurodegenerative diseases using human neuroblastoma SH-SY5Y cells. Recent evidence indicates that hypoxia-inducible VEGF has neurotrophic and neuroprotective effects on neuronal and glial cells. Therefore, we investigated the effect of coffee on the VEGF expression and found that even low concentration of coffee (<2%) strongly induced VEGF expression via an activation of HIF1a translocation into nuclei. The activation of HIF1a by coffee was attributed to the coffee-dependent inhibition of prolyl hydroxylation of HIF1a, which is essential for proteolytic degradation of HIF1a. Next, we investigated the effect of coffee on the amyloid b (Ab) production in SH-SY5Y cells and found Ab production was reduced by 20% after 24hr treatment with 2% coffee. Furthermore, the reduction was attributed to the reduction in BACE1 activity which is rate limiting for Ab production. The reduction in BACE1 activity was revealed to be due to proteasomal degradation induced by coffee. Coffee component(s) responsible for the activation of HIF1a and BACE1 degradation was not major constituents such as caffeine, caffeic acid, chlorogenic acid and trigonelline, but was found to emerge during roasting process. Our results suggest that daily consumption of coffee may induce VEGF expression and reduce Ab production in neuronal cells. These might be related to protective effect of coffee on neurodegenerative disorders such as Alzheimers disease and Parkinsons disease.

A Promising Phospholipase A2-Targeted Peptide Slowing Amyloid Beta Pathology in an Alzheimer’s Disease Mouse Model

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Abstract

Alzheimer's disease (AD) treatment is a challenge up to now, no new drug being approved by the FDA since 1993, while the current therapies are only symptomatic. In this context, a phospholipase A2 (PLA2) targeted peptide has been developed by our group aimed to reversibly and specifically modulate this enzyme involved in AD-associated signaling pathway dysregulation. The existing PLA2 inhibitors show protection against apoptosis by amyloid beta (Aβ) but are irreversible.

Our PLA2-targeted peptide (PLP25) was coupled to a peptide able to cross the blood-brain barrier (LRP2) in order to improve its brain availability and this complex (PLP25-LRP2) was tested in vitro and in vivo. PLP25-LRP2 reduces arachidonic acid (AA) release from PLA2-stimulated cells and blocks PLA2 translocation to cell membranes. This inhibition was indirectly propagated to related enzymes such as cyclooxygenases and lipoxygenases due to lower levels of AA. Filopodial dynamics and actin cytoskeleton reorganization were also modulated by PLP25-LRP2, phenomena associated to neuronal excitotoxicity. In vivo, PLP25-LRP2 seems to improve spatial memory of AD mouse model in the Barnes maze as compared to a non-specific peptide (NSP). Interestingly, treated mice exhibit a lower number of amyloid plaques, shown by molecular magnetic resonance imaging and immunohistochemistry, present a cellular localization of phosphorylated tau comparable to healthy mice, and expression levels of PLA2 and NMDA receptors restored to control levels.

Taken together, our results reveal the potential of our complex to be an original therapeutic strategy in AD.
Validation of Blood-Based Biomarkers for the Diagnosis of Early Alzheimer's Disease (Ad) in Clinical Addia Chronobiology and Proof-of-Performance Studies

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16ADDIA consortium

Abstract

There is an unmet need for an accurate, non-invasive biomarker test for the diagnosis of early Alzheimer's disease (AD). The objectives of the ADDIA program are the analytical validation and the proof-of-performance of a) two erythrocyte biomarkers, using specific fluorescent probes and b) circulating biomarker panels, including mRNA, miRNA, lncRNA signatures, protein panels, for AD diagnostic purposes.

Methods: The ADDIA chronobiology study is a monocentric study recruiting 12 patients with mild or moderate AD and 12 healthy control subjects; the ADDIA Proof-of-Performance (PoP) study is a multi-centric study recruiting 800 subjects into 3 groups: AD patient group (200 early AD and 200 late AD), a group of 200 patients with non-AD dementia (NAD) and 200 healthy controls. During the screening period, neurocognitive assessment, brain MRI data in all subjects, and the CSF biomarker data in AD and NAD groups are collected. During the visit(s), samples including blood and its components are obtained.

Results: The results of the chronobiology study on diurnal impact on biomarkers will be presented. The ADDIA PoP study is expected to be completed by June 2019 and will provide the first large data sets on the performance of the tested biomarkers, and their correlation to neurocognitive, imaging scores or CSF biomarkers. The most accurate biomarker combination will be selected for use as Research-Use-Only test and for submission to regulatory agencies for approval as an in-vitro diagnostic (IVD) tool for the context of use of diagnostic of AD, differential diagnostic. The other future clinical applications are for prognostic or theragnostic purposes.
Role of P-glycoprotein inhibitors in children with drug resistant epilepsy

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Abstract

Objective: The application of P-glycoprotein (Pgp), one of the known multidrug transporters, has been suggested in the treatment of drug resistant epilepsy (DRE). The following study aimed to measure the serum level of Pgp as a possible indicator of tissue Pgp over expression in patients with DRE and to assess the efficacy of Verapamil (as a Pgp inhibitor agent) in these patients.

Material and Methods: A group of 24 patients with DRE were recruited and subdivided into two groups, one receiving Verapamil and the other a placebo in a double-blind randomized study. Pgp Serum levels were measured at enrollment and 12 months later. Twenty medically controlled epileptic patients served as a control group.

Results: A significant statistical difference was found between the Pgp level of patients and the control group, with levels being elevated in the former. Patients on both verapamil and the placebo showed improvement in seizure frequency and severity.

Conclusion: Pgp serum levels in patients with DRE were significantly elevated compared to patients with medically controlled epilepsy. The effect of verapamil as Pgp inhibitor on DRE requires further evaluation and research.

4.5-6 Hz Theta Sub-Band Energy Sensitivity and Somatosensory Cortex Activity in Patients with Full-Face Lesions

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Abstract

In this study, EEG based analysis of somatosensory cortex activities related to the lesion was aimed in patients with full face lesions. Four full-face lesions patients and 10 volunteers participated in the study. 64 channel EEG measurements were performed by brush stimulation of the right hand, left hand, right lower face and left lower face sites. Stimulations were carried out in 3 parts including stimulation and rest. Each block lasted for 28 seconds, resulting in an overall duration of 168 seconds for each sites. EEG signals were separated at 8 levels using wavelet packets and 4.5-6 Hz theta sub frequency energy values were compared. In this band, the mean and standard deviation values of healthy group were RH = 0.54 ± 0.13, LF = 0.57 ± 0.14, RF = 0.64 ± 0.25, LF = 0.59 ± 0.09, whereas in patients with facial lesions RH = 1.80 ± 0.65, LF = 1.62 ± 0.34, RF = 1.46 ± 0.5, LF = 1.42 ± 0.43. Theta activity in the 4.5-6Hz band is high in four different stimulus sites in patients with facial lesions. This dominance is spread to the CP, P and PO regions on both sides, and the right side is more dominant. As a result of this study, we think that the 4.5-6 Hz subband theta activity contains significant differences in the group with facial lesions and may be considered as a sign of the presence of the lesion. We are continuing our studies with EEG-fMRI correlation.

Funding: This study is funded by a grant from the Scientific and Technological Research Council of Turkey (Project no: 117E818) and by Akdeniz University, Scientific Research Projects Supporting Unit.

Biography

Professor Colak completed his doctoral studies in the field of signal processing. Afterwards, he studied autonomous nervous system at University of Technology Zurich and motor control and synaptic balance at Neuroscience Institute of Universite Rene Descartes, Paris. He is the responsible director Neuroscience Laboratory of Dept. of Electrical Eng., Akdeniz University. He is working on the analysis of motor and sensory cortex changes and brain plasticity in facial transplantation, arm transplantation, arm replant patients and amputees and developing new rehabilitation processes. In addition, he continues to develop mathematical solutions and interfaces in the fields of EEG, EMG, fMRI and TMS.
Dopaminergic Signaling in Prefrontal Cortex Contributes to the Antidepressant Effect of Electroacupuncture: An iTRAQ-Based Proteomics Analysis in a Rat Model of CUMS

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Abstract

Electroacupuncture (EA) is used as an adjunctive treatment for depression. However, the mechanistic basis for its effects is unknown. This was investigated in the present study by evaluating the efficacy of the EA/paroxetine combination (EA+P) in a rat model of depression caused by chronic unpredictable mild stress (CUMS) through behavioral testing, transmission electron microscopy (TEM) analysis of synapse morphology in the prefrontal cortex (PFC), and isobaric tags for relative and absolute quantitation (iTRAQ)-based proteomic analysis of differentially expressed proteins in the PFC. We found that EA+P treatment for 1 week significantly relieved depression-like behaviors; this was accompanied by changes in neurodegenerative morphology such as neuron loss and synapse morphology in the PFC, as observed by TEM. Additionally, iTRAQ analysis showed that dopaminergic signaling was significantly altered in CUMS rats following EA+P treatment; this was due to changes in the expression of critical enzymes in this pathway—namely, aromatic-l-amino-acid decarboxylase and tyrosine 3-monooxygenase, which was confirmed by western blotting. These results suggest that EA combined with paroxetine exerts antidepressant effects via modulation of dopaminergic signaling in the PFC neuron and thus has clinical potential for the treatment of depression.

Immune Markers in the Blood of Patients with Frontotemporal Dementia

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Abstract

The aim of this study was to identify a number of markers of inflammation in the blood of patients with frontotemporal dementia (FTD).

Material and Methods: 34 patients with FTD were examined. The diagnosis of FTD was established according to the diagnostic criteria of the International consortium 2011. The control group consisted of 35 people, comparable in age and sex with patients with FTD. Blood plasma was used for immunological studies. The enzymatic activity of leukocyte elastase (LE) and the functional activity of α1-proteinase inhibitor (α1-PI) were determined by spectrophotometric method, the concentration of interleukin-6 (IL-6) and C-reactive protein (CRP) were measured by enzyme immunoassay.

Results: A significant increase in α1-PI activity in patients with FTD compared with the control was detected (p<0.001) The other indicators did not differ from the control ones. However, a significant variation of all studied parameters was revealed, both excess and decrease of values relative to the control. For example, variation of LE activity was from 127 to 276.5 nmol / min-ml. According to level/activity of inflammation markers, two immunophenotypes were identified: 47% of patients with FTD are characterized by a proinflammatory immunophenotype with an increase in inflammatory marker values, and 53% of patients with FTD are characterized by a proinflammatory immunophenotype with insufficient neutrophil activity (by LE activity), similar to Alzheimer’s disease.

Conclusion: The findings indicate the involvement of inflammatory reactions in the development of FTD and the heterogeneity of this dementia in terms of immunological parameters.

Key words: frontotemporal dementia, markers of inflammation; leukocyte elastase, interleukin-6, acute-phase proteins.

Pattern of Neurological Manifestations among SLE Patients in Aseer Central Hospital

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Abstract

Background: Systemic lupus erythematosus (SLE) is one of worldwide autoimmune disorder that has a significant mortality and morbidity. Neurological manifestations are less prevalent in other systemic inflammatory and autoimmune disorders.
**Aim:** To assess pattern and determinants of neurological manifestations among SLE patients admitted to Aseer Central Hospital (ACH).

Methodology: A record based retrospective study was conducted by reviewing all medical records of SLE patients admitted to Aseer Central Hospital (ACH) during the period from 1994 to 2018. A total sample of 230 patients' files with complete data were reviewed and included in the study. The data were extracted using pre-structured format covering bio demographic and neurological data.

**Results:** A total sample of 230 SLE patients with ages ranged from 15 years to 71 years old and mean age of 35.5 ± 11.3 years old. Females constituted 93% of the sampled patients. Neurological manifestations was recorded among 23.5% of the patients. Headache was the most frequently recorded neurological complain (68.5% of patients with neurological symptoms) followed with seizures (22.2%), stroke (15.5%) while mood disturbance was the least recorded manifestation (3.7%).

**Conclusions & recommendations:** In conclusion, nearly one out of each four SLE patients experienced at least one type of the neurological manifestations specially headache. Neurological complaint were more common among old aged patients with long disease duration. More care for these manifestations should be paid for early diagnosis and management.

Keywords: Systemic lupus erythematosus, SLE, Manifestations, Neurological signs, CNS manifestations

**Alzheimer’s Disease Markers in Age-Related Cataracts and Retinas From Diabetic Patients**

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**Abstract**

AD is the most common cause of dementia and it is characterized by the formation of senile plaques and neurofibrillary tangles. Senile plaques are extracellular and intracellular deposits of amyloid beta peptide 1-42 (AB42) and amino truncated species peptides ABN 3-42 and ABN 11-42. These peptides cause neuronal and synapse loss. It has been recognized that accumulation of AB42 also occurs in eyes of age-related macular degeneration and eyes from AD patients. Age-related cataract (arc), the opacificication of the crystalline lens is one of the leading causes of blindness in the world. There is no information available about the presence and the relevance on N-truncated species in ARC and retinas from diabetic and no diabetic patients. AIM: The aim of this study was to determinate the presence of AB species in anterior lens capsule, cataract nuclei and retina from diabetic (DP) and no diabetic patients (NDP) with ARC.

**Methods:** Informed consent was obtained from all patients. Samples were collected from 30 age-related cortical cataract and diabetic patients over 50 years of age with LOCS II score of nuclear color ≥ 4 along with 30 agerelated from no NDP after phacoemulsification surgery. Lens capsules, cataract nuclei and retinas were processed for IMH and IF. Anti-AB42, anti-ABN 3-42 and anti-ABN11-42 were used to detect these peptides and preparations were observed by confocal microscopy. For WB assays, 3 capsules and cataract nuclei were collected from each group and pooled for protein quantification.

**Results:** IMH, and WB assays show the presence of ABN3-42 and ABN11-42 peptides in anterior lens capsule, nuclei of cataract and retinas from DP and NDP. Surprisingly, there is a major accumulation and production of ABN3-42 in capsule lens cells from ARC than DP. Conclusions. For our knowledge, this is the first time showing the presence of ABN3-42 and ABN11-42 in tissues affected by the development of ARC from diabetic patients, such as retina and lens capsules of the eye. These N-truncated species are more toxic and more prone to aggregate inducing a pro-inflammatory state. There are differences on the intracellular distribution of both peptides in retina and lens capsule from ND and DM patients. AHT affects the deposition of ABN3-42, which suggests that metabolic and physiological state affect the distribution of these peptides. The detection of these peptides in the retina and lens capsules could be used as an early marker of neurodegenerative disease such as AD because retina is a direct link between brain and eyes and it is considered a window to the brain. However more studies are needed in order to prove it.
Gene Environment Interactions in Alzheimer’s Disease Highlight an Important Role for Infection and Multiple Endogenous Antimicrobial Agents Other Than Aβ

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Abstract

Gene-environment interactions were studied for 1591 Alzheimer’s disease (AD) susceptibility genes (GWASdb) in relation to other GWASdb disease genes, chemicals (Comparative Toxicogenomics Database) and host genes used by pathogens, using enrichment analysis. AD genes were enriched in brain, immune system, microglia and barriers and in host gene products related to 18 pathogens. They were enriched in genes for type 2 diabetes, cardiovascular diseases, lipid metabolism disorders, arteriosclerosis, obesity, mood disorders and immune system or infection, all previously linked to AD. Enrichment was also seen in cancer genes, a disease which inversely associates with AD. Genes affected by NSAID’s, statins, antidiabetics (PPAR ligands) and dietary polyphenols with antimicrobial activity were also enriched in AD genes. Endogenous compounds related to the effects of AD gene products included retinoids, estrogens, progesterone, corticosterone, calcitriol, vitamin C and D3, folate, methionine and choline, an endogenous aryl hydrocarbon receptor ligand (ITE) and oxidative stress related compounds. Most could be linked to immune regulation and many, like beta-amyloid, have antimicrobial properties (N-acetyl cysteine, Glutathione, Lithocholic acid, melatonin, Nitric oxide, iron/ascorbic acid, iron/O₂, H₂O₂, arachidonic and hypochlorous acids). AD genes were also enriched in genes affected by AD risk factors (fats/sucrose, pesticides, metals, vehicle emissions or smoking and other pollutants). The analysis highlights AD gene subsets related to AD comorbidities, risk factors or beneficial agents. Endogenous chemicals targeted by the AD genes are dedicated to the immune system and specifically to antimicrobial defence. Antimicrobial drugs may aid these endogenous agents and might also be of benefit in AD.

Biography

After a degree in Zoology, I switched to Pharmacology (Leeds, Bradford and Bristol) ending up heading a Neuroscience genomics group at Synthelabo in Paris (now Sanofi). I am now retired and work from home using “Big data” publicly available on the web to analyse gene/environment interactions in silico in relation to neurological and psychiatric disorders. I also curate a website (PolygenicPathways) recording genes and environmental risk factors related to these conditions. This also contains a number of host/pathogen interactomes.

Mild Cognitive Impairment and Progression To Dementia of Alzheimer’s Disease

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Abstract

The elevation of life expectancy in the Brazilian population raises questions about the preparation of the public health system in identifying elderly patients with signs of cognitive impairment. Currently, as consequence of the long duration of preclinical...
Alzheimer’s Disease has been a major point of emphasis early preventive efforts may be more effective in detection preclinical manifestation of the AD. Clinical dementia presents an important impact on the individual caregivers, on the family, society and economy. Identifying individuals that already present some cognitive impairment, although they remain functional, as well as analyzing associated comorbidities constitute opportunities to analyze possibilities for future interventions. Dementias are diseases that impose a burden to the health systems with high costs whereas the identification of individuals with cognitive impairment without dementia can aid in future planning on the part of the carriers themselves and of their families, enabling the mitigation of costs. This narrative revision can aid general practitioners to have greater contact with this theme.

**Keywords:** Elderly, Cognitive deficits, Mild Cognitive Impairment, General Practice, Alzheimer’s disease, Diagnosis

**Biography**

Ana Beatriz Steiner has degree in medicine from the Regional University Foundation of Blumenau, Santa Catarina, Brazil, Medical Residency in Psychiatry from Hospital Santa Catarina in Blumenau and Specialization in Geriatric Psychiatry at Federal University of São Paulo. Master in Health Sciences from the Federal University of São Paulo. She is pursuing her PhD from the Center for Economics in Mental Health (CESM), Department of Psychiatry Federal University of São Paulo. Her research interest includes: mild cognitive impairment, diagnosis of dementia syndromes in primary care, health care costs of individuals with dementia and informal care costs.

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**Early Oligomeric Aggregates of the Alzheimer Peptides Aβ (1–40) and Aβ (1–42)**

**Jana Wägele*, Silvia De Sio and Maria Ott**  
*Martin-Luther University Halle-Wittenberg, Germany*

**Abstract**

Due to their role in cytotoxicity and neuronal apoptosis, low-molecular-weight aggregates of the Alzheimer’s amyloid-β peptide have attracted increasing interest. One of the main techniques to characterize such intermediate states of the aggregation of amyloidogenic peptides is fluorescence spectroscopy.

We studied the effects of four of the most commonly used fluorophores on the aggregation of Aβ-peptides using time-resolved and single-molecule fluorescent spectroscopy, x-ray diffraction, transmission electron and atomic force microscopy [1]. While we found the fluorescent tags to affect only slightly the final fibrillar structure, there are significant differences of the sizes of the oligomeric species detected depending on the chosen fluorophore.

In particular, we relate the presence of high-molecular-weight oligomers of Aβ (1–40) to net-attractive, hydrophobic fluorophore-peptide interactions. In the absence of significant attractive fluorophore-peptide interactions Aβ (1–40) displays low-molecular-weight oligomers only, which is in contrast to the disease-relevant peptide Aβ (1–42). The latter develops high-molecular-weight oligomers even when labeled with the least interacting fluorescent tag. Moreover, recent results could demonstrate how aggregation conditions sensitively modify the oligomer sizes of Aβ (1–42), which is a direct evidence for different pathways of aggregation as proposed earlier.


**Biography**

Jana Wägele studied physics in Bonn, Uppsala and Halle and is currently working on her Ph.D. thesis at the Martin-Luther-University in Halle, Germany. Her research interests are the early stages of amyloid formation and the underlying mechanism of aggregation with the focus on the Alzheimer peptide.
New Strategies for Alzheimer’s Disease Diagnostic Using Peripheral Cells. The Mitochondrial Approach

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Abstract

Alzheimer’s disease (AD) is a neurodegenerative disorder and the most common form of dementia. AD is characterized by brain presence of senile plaques, which are formed by aggregates of Aβ peptide and the neurofibrillary tangles (NFTs), formed by pathological forms of tau protein. Evidence suggests that these elements affect neuronal population compromising energy supply, antioxidant response, and synaptic activity. AD principally affects the memory and the cognitive functions of the patients, and currently successful strategies for diagnosis and early treatment are lacking. In this scenario, accumulative evidence suggests that mitochondrial dysfunction precedes the establishment of tau and Aβ pathology and contributes to synaptic degeneration observed in AD. Therefore, reducing mitochondrial injury may have beneficial effects for synaptic and neuronal dysfunction, which later could improve memory and cognitive impairment observed in AD patients. Interestingly, the examination of peripheral cells from AD patients also presents specific signs of mitochondrial dysfunction, suggesting that these mitochondrial defects could be a potential mechanism of early diagnostic of the disease. In conclusion, mitochondrial injury is an important factor in the pathogenesis of AD, and the study of this process in peripheral cells could reveal new strategies to mitigate neurodegeneration and to develop new diagnostic methods for an early detection of AD.

Biography

Dr. Quintanilla has been working at Universidad Autonoma de Chile since 2014 and became Associate Professor in 2015. He developed a Postdoctoral Research at University of Alabama at Birmingham (UAB) (2005-2008) and University of Rochester Medical Center (2008-2012) at USA. In 2014 he established his laboratory at Universidad Autonoma de Chile, Santiago, Chile in where his group have been working in the role of mitochondrial dysfunction and tau pathology in the pathogenesis of Alzheimer’s disease. Also, Dr. Quintanilla has study the contribution of mitochondrial failure to Huntington Disease and lately he established a new research line about the role of mitochondria in alcohol neurotoxicity induced by alcohol consumption.

Effect of Alzheimer’s Disease on Processing Levels in Language Production in Bilingual

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Abstract

The advancement in age affects the good mastery of two languages. This deficit can be noticed at bilingual patients with Alzheimer’s disease. The linguistic deficit is the most frequent cognitive disturbance after memory disorders in AD semiology. In addition, most of the studies dealing with the linguistic semiology of the AD were essentially interested in describing the linguistic behavior of the monolingual people, and based on modest samples. As a result, the localization of disturbed processing levels in language production of bilingual Alzheimer’s patients can better help us describe language aging in Alzheimer’s disease. The objective of the present study is to locate the disturbed levels of processing in language production of bilingual Alzheimer’s patients by analyzing the discourses of 120 subjects including 60 bilingual patients with Alzheimer’s disease and 60 healthy bilinguals.

The obtained results determine a lexical-semantic disturbance in the first language (L1). On the other hand, the syntactic level seems rather affected in the second language (L2) and relatively spared in the first language (L1). The syntactic aspects of the L1 are more resistant because they depend on the procedural memory preserved in the MA. Whereas the syntactic aspects of L2 and the lexical-semantic aspects of L1 would be disturbed because they are part of the declarative memory that has been early altered.

Key words:
Alzheimer’s disease, levels of processing in language production, bilingualism
Senataxin Deficiency Causes DNA Damage and Selective Degeneration of Motor Neurons in Spinal Muscular Atrophy

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Abstract

Spinal muscular atrophy (SMA) is caused by the chronic low levels of survival motor neuron (SMN) protein and is characterized by degeneration of spinal cord motor neuron. SMN is a ubiquitously expressed protein and is essential for cell viability. Molecular mechanisms of selective degeneration of motor neurons caused by deficiency of ubiquitously expressed SMN protein is unclear. To unravel the molecular mechanism of selective degeneration of motor neurons in SMA, we tested the hypothesis that the deficiency of a ubiquitous protein, SMN, may cause a common biochemical defect in all cell types, but which might specifically affect a neuron-specific process, leading to selective degeneration of motor neurons in SMA. We report that chronic low levels of SMN cause Senataxin-deficiency, which results in increased RNA-DNA hybrids (R-loops) and DNA double-strand breaks (DSBs), and deficiency of DNA-activated protein kinase-catalytic subunit (DNA-PKcs), which impairs DSB repair. Consequently, DNA damage accumulates in patient cells, SMA mice neurons and patient spinal cord tissues. In dividing cells, DSBs are repaired by homologous recombination (HR) and non-homologous end joining (NHEJ) pathways, but neurons predominantly use NHEJ, which relies on DNA-PKcs activity. In SMA dividing cells, HR repairs DSBs and supports cellular proliferation. In SMA neurons, DNA-PKcs-deficiency causes defects in NHEJ-mediated repair leading to DNA damage accumulation and neurodegeneration. Complementation with SMN rescues DNA damage in SMA neurons and patient cells. Moreover, Senataxin overexpression in SMA neurons reduces R-loops and DNA damage, and rescues neurodegeneration. These findings suggest that Senataxin may be a potential SMN-independent modifier of SMA.

Biography

Associate Professor of Molecular and Translational Medicine, Paul L. Foster School of Medicine at the Texas Tech University Health Sciences El Paso in El Paso, Texas. A Cell and Molecular Biologist by education and training, received Ph.D. from the University of Delhi, India and postdoctoral training at the University of Massachusetts School of Medicine, MA, USA. Research interests include investigation of the molecular mechanisms of neurodegeneration associated with the pathogenesis of neuromuscular disorders, including spinal muscular atrophy and amyotrophic lateral sclerosis. We identify, characterize and validate molecular targets as potential therapeutic targets using genetic and pharmacological methods.

Parkinson's Disease Detection at an Early Stage Using Voice

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Abstract

Vocal impairments, characterized by hypokinetic dysarthria, are among the earliest symptoms in Parkinson’s Disease (PD). We recorded and analyzed voice of 122 male French speakers, among them 74 recently diagnosed with PD and 48 healthy controls. They performed speech tasks such as sentence repetitions, reading, free speech, sustained vowels, fast and slow syllable repetitions, during 15 min. The participants were recorded with a high quality microphone at Pitié-Salpêtrière Hospital in Paris, and at their home with their own telephone as they called an interactive answering machine. For the analysis we adapted a method classically used in speech and speaker recognition, based on Mel-Frequency Cepstral Coefficients (MFCC) extraction and Gaussian Mixture Model (GMM). We classified early PD subjects from controls with an accuracy of 83%, at the EER threshold, using recordings obtained with the
high quality microphone, and an accuracy of 75% with the telephone recordings. We assessed the impact of several factors on the classification performances, such as specificity and quantity of speech tasks, channel and environment effects. As far as we know, this is the first time that audio recordings from telephone network have been used for early PD detection. This is a step forwards a potential future Parkinson’s disease diagnosis and telediagnosis tool based on voice.

**Biography**

Laetitia Jeancolas is a PhD student from Telecom SudParis in Université Paris Saclay, and a former student of Ecole Normale Supérieure. Her PhD project deals with the early detection of Parkinson’s disease (PD) through voice analyses, and the neural correlates of PD voice impairments. Her research interests are more widely the use of signal processing and neuroimaging techniques for the early detection of neurodegenerative diseases and the understanding of their mechanism.

**Withdrawal and Ageing**

*Hanon Cécile*, Hugonot-Diener Laurence, Kruczek Elisabeth, Gauillard Jacques

**Abstract**

The concept of withdrawal and aging are combined in several ways and have different semiological aspects. Old age is a period of life favorable to withdrawal. In our western societies, where the representation of old age borders on blissful ageism, it is not good to “get old”. However, withdrawal is intimately linked to the aging and social life of the latter.

The communication will discuss the different stages and possibilities of withdrawal and how social withdrawal takes shape with the empty nest syndrome, at the time of the departure of the children and the beginning of the retirement.

Moreover, sensory aging can lead to social isolation and it is important to overcome these sensory failures in order to remain connected. Taste, smell, touch, vision and hearing are no longer as effective in maintaining the relational link and the pathologies of disaffection contribute to reinforce social withdrawal.

We will also address neurodevelopmental approaches of pathological withdrawals, such as

**The Role of Physiotherapy to Prevent Fall in Parkinson’s Disease. A Scoping Review**

Salem F. Alnosirate

*University of Tabuk, Saudi Arabia*

**Abstract**

**Background:** Parkinson's disease is considered a neurological disease with high prevalence rate among population. One of its main problems is recurrent fall which has numerous contributing factors such as history of fall, impaired balance, poor functional mobility, gait deficits, muscle weakness, fear of falling and depression.

**Aim:** To review physiotherapy effect on fall incidence, near fall incidence and several fall risk factors including balance, gait, functional mobility, fear of falling, and muscle weakness by reviewing related randomized controlled studies by using Arksey and O’Malley.

**Method:** A scoping review was led dependent on Arksey and O’Malley4. This paper based on this structure to perceive intervention studies have been embraced in physiotherapy to prevent fall after Parkinson disease. The search included various databases. The referencing arrangements of every pertinent paper were additionally filtered for more studies.

**Findings:** 173 articles were included, thirty-three of which met the eligibility criteria. Thirteen studies reported on the direct impact of physiotherapy on fall, while the rest examined the impacts of physiotherapy on factors that are associated with fall. Different outcomes, interventions types and duration were used in these studies. All papers showed favorable result of physiotherapy on fall and near fall incidence, balance, gait, functional mobility, muscle strength and fear of falling.

**Conclusion:** Physiotherapy has the possibility to decrease fall incidence and fall risk in people with Parkinson disease (PD), but more studies is needed on long term effect and best intervention.
Dermatoses in Parkinsonism: The Importance of Multidisciplinary Follow-Up

Thereza Cristina d’Ávila Winckler*, Isadora Antunes, Kátia Sheylla Malta Purim, Luara Leticia Grande Nathália Cristina Alberton and Tatiana Francinne Regis Navarro

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Abstract

Parkinsonism, a common neurodegenerative disorder, is characterized by bradykinesia with rigidity and/or resting tremor, in addition to non-motor symptoms, which include dermatological manifestations. The objective of this study is to evaluate the main dermatoses in patients with parkinsonism found at the Philanthropic Association of Curitiba - PR. A cross-sectional descriptive study was carried out with the application of a questionnaire and dermatological evaluation of the patients. The sample consisted of 386 patients and was composed mainly by men (55.4%), between 60-74 years old (51.6%), with complete primary education (45.3%), disease diagnosis time between 5-10 years (35%) and in use of medication (96.6%). The most prevalent dermatoses were pigmented nevus (36.3%), warts (25.1%), actinic keratosis (22%), seborrheic keratosis (21.5%), seborrheic dermatitis (20.5%), and rosacea (19.2%). Among the 13 cases (3.4%) of malignant cutaneous neoplasms confirmed by biopsy, 2 were melanomas. Regarding patients’ sex, there was a higher prevalence of inflammatory dermatoses (OR 1.64, 95% CI 1.08-2.51, p = 0.025) and benign cutaneous neoplasms (OR 1.77, 95% CI 1.16-2.69, p = 0.01) in men. As to age, patients aged between 60-74 years had more pre-malignant skin lesions (OR 2.60, 95% CI 1.05-6.44, p <0.001) and seborrheic keratosis (OR 2.52, 95% CI 1.02-6.25, p = 0.001) and, in those older than 75 years, actinic keratosis was more frequent (OR 5.43, 95% CI 2.17-13.6, p <0.001). The results of the study show that it is fundamental to dermatologically evaluate and monitor these patients, aiming at diagnosis and early treatment of lesions, especially of skin cancer.

Biography

Thereza Cristina d’Ávila Winckler, was born in Florianopolis, south of Brazil where she studied medicine at Federal University of Santa Catarina (UFSC). After her training in medicine, she performed his residence in Neurology at the Public Servant Hospital of São Paulo and get her Master degree in Neurology at Paulista School of Medicine. She was supervisor of the Medical Residency Program in Neurology at the Red Cross Hospital, Curitiba. Former Professor of Neurology at the Pontifical Catholic University of Parana and currently Professor of Neurology at the Positivo University.

Network Analysis of Patents and Publications’ Activity on Parkinson’s Decease

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Abstract

Recently developed network analysis algorithms were applied for publications and patents (items) databases on different aspects of Parkinson’s disease (PD).

Methods of network analysis including centrality indices are used. Networks of items are modeled as graphs, where the nodes are identification numbers of items, and the edges of the graph carry the information about the citations between items. New approaches and methods of centrality analysis are used to identify pivotal studies - Short-Range Interaction Centrality (SRIC) and Long-Range Interactions Centrality (LRIC), which take into account the characteristics of nodes, long distance interactions between nodes and, most importantly, the influence of groups on individual nodes. The developed models of network analysis allow to attract researchers attention on various aspects of Parkinson’s disease to obtain information on key research areas, and to rank them by importance. The obtained results allow to track changes in specific areas of various development subjects and to draw attention to previously unknown patents and developments.
The Utility of FDG-PET Imaging in Differential Diagnosis of Parkinsonism

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Abstract

Introduction: Differential diagnosis of parkinsonian disorders can be difficult on clinical grounds, especially in the early stage. Recent advancements in 18-F-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging reveals different patterns of regional glucose metabolism in idiopathic Parkinson’s disease (IPD) and atypical parkinsonian syndromes, such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS), which may help differentiating between these conditions.

Purpose: To assess the utility of FDG-PET imaging in differential diagnosis of Parkinsonism in clinical practice.

Methods: FDG-PET was performed in 72 patients with parkinsonism (age 34 to 80) referred to our Center by movement disorder specialists. FDG-PET diagnosis was obtained by visual assessment of individual scans combined with voxel-based statistical parametric mapping analysis. FDG-PET diagnosis assigned at the time of imaging was compared with the final clinical diagnosis made after ≥2 years follow-up.

Results: IPD is characterized by preserved and pronounced glucose metabolism in the basal ganglia with preserved cortical metabolism, or reduced cortical metabolism frontal parietal and posterior parietotemporal in the patients with cognitive disorders. MSA is characterized by hypometabolism in the striatum, especially putamen, cerebellar and brainstem level (pons). In PSP hypometabolism is found frontal (medial, basal, lateral premotor), striatal (caudate), thalamic and midbrain. CBD is presented with asymmetrical cortical and subcortical hypometabolism, most notably frontoparietal, in the hemisphere contralateral to dominant clinical symptomatology. FDG-PET findings were consistent with IPD in 27/29, MSA 18/20, PSP 19/21, CBS 2/2. Concordance between the FDG-PET and clinical diagnoses was 92% in the overall sample (IPD 93%, MSA 90%, PSP 91% and CBS 100%). The diagnostic accuracy of FDG-PET was 93% for IPD and MSA and 97% for PSP.

Conclusion: FDG-PET may help differentiate between IPD, MSA, PSP and CBS among patients presenting with parkinsonian symptoms, which is important for patient counselling and making early decisions about treatment.

miR-455-5p Downregulation Promotes Inflammation Pathways in the Relapse Phase of Relapsing-Remitting Multiple Sclerosis Disease

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Abstract

MicroRNA-455-5p seems to have an anti-inflammatory role in the immune system since its expression is induced by IL-10 cytokine. Multiple sclerosis (MS) is a chronic demyelinating neurodegenerative disease of the central nervous system that is caused by an autoimmune inflammatory attack against the myelin insulation of neurons. The expression level of miR-455-5p and its role in MS pathogenesis has yet to be elucidated. We found that miR-455-5p expression was highly correlated with disease severity in MS patients. MiR-455-5p expression inversely correlates with its inflammatory predicted targets (MyD88 and REL) in relapse and remitting-phase
patients. Luciferase assays confirm that MyD88 and REL are direct targets of miR-455-5p. This study represents the first report of the miR-455-5p act as an anti-inflammatory role in MS, at least partially through targeting MyD88 and REL. This study may provide important information for the use of miR-455-5p as a novel strategy to improve the severity of disease and control inflammation and attack in MS patients.

**Biography**

Mona Tamaddon is a first-year Ph.D. student in Cellular and Molecular Biology at Tehran North Azad university. She holds an M.S. in Molecular Genetic and Her thesis work focused on investigating the correlation of oncogenic miRNAs with endogenously master regulator of APA, CFIm25 in breast cancer patients and exploring the functional role of these miRNAs in breast cancer cell line. Her main research interest centers on gene regulation mechanisms and its deregulation in cancers and autoimmune diseases.

**Model for Prediction of Progression in Multiple Sclerosis**

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**Abstract**

Multiple sclerosis is an idiopathic inflammatory disease of the central nervous system and the second most common cause of disability in young adults. Choosing an effective treatment is crucial to preventing disability. However, response to treatment varies greatly between patients. Because of this, accurate and timely detection of individual response to treatment is an essential requisite of efficient personalised multiple sclerosis therapy. Nowadays, there is a lack of comprehensive predictive models of response to individual treatment.

This paper arises from the clinical need to improve this situation. To achieve it, all patient's information was used to evaluate the effectiveness of demographic, clinical and paraclinical variables of individual response to fourteen disease-modifying therapies in an international cohort. A personalized prediction model to three stages of disease, as a support tool in clinical decision making for each MS patient, was developed applying machine learning and Big Data techniques. These techniques were also used to reduce the data set and define a minimum set of characteristics for each patient. Best predictors for the response to treatment were identified to refine the predictive model. Fourteen relevant variables were selected. A web application was implemented to be used to support the specialist neurologist in real time. This tool provides a prediction of progression in EDSS from the last relapse of an individual patient, and a report for the medical expert.

**Biography**

**Cristina Pruenza García-Hinojosa** is Degree in Mathematics and Computer Engineer, Ms Degree in Computer Science and Ms Degree in ICT Research and Innovation in Computational Intelligence both from Universidad Autónoma de Madrid (UAM-Spain). At present she is Senior Data Scientist and Technical Leader in a private R&D+i institution named Instituto de Ingeniería del Conocimiento (IIC-UAM) dedicated to extracting knowledge on the basis of high volumes of heterogeneous data (Big Data) and optimizing business processes in areas such as healthcare and energy. Pruenza García-Hinojosa has experience in scientific computing, mathematical and statistical modeling, data analysis and wind production forecast. She has participated in several projects related to e-Health and in the ADNI project research on Alzheimer's and some possible tools to treat MRIs.