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Monocyte biomarkers define sargramostim treatment outcomes for Parkinson's disease

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Clinical and pathobiological diversity of Parkinson's disease (PD) presents a major challenge in the development of relevant biomarkers to monitor disease progression and disease-modifying therapies. The dysregulation of innate immunity is involved in both the development and progression of PD through impairments in monocyte activation, function, and secretion. Based on such and after assisted leukapheresis and centrifugal elutriation, changes in pure populations of monocyte-macrophage were evaluated for gene and protein expression in five PD patients. These studies were performed before and two and six months during the course of immune modulatory neuroprotective granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim, Leukine®) therapy. Transcriptome and proteome biomarkers were scored against clinical motor function. Pathway enrichments from single cell-RNA sequencing and proteomic data sets presented disease-relevant biomarkers of antioxidant, anti-inflammatory, and autophagy genes and proteins. These included, but were not limited to, LRRK2, HMOX1, TLR2, TLR8, NF-κB, Atg7, and GABARAPL2. Sargramostim therapy now provides a monocyte signature capable of scoring clinical motor functions during disease-linked immune transformation therapy.

Biography

Mai Abdelmoaty is a PhD candidate in University of Nebraska Medical Center (UNMC, USA). She started her career in 2007 as a Pharmaceutical Researcher at National Research Centre (Egypt). She got MSc in Biochemistry (Ain Shams University, Egypt) in 2012. She was a Fulbright scholar at UNMC in 2016 before starting her PhD studies in 2017. She worked as a Teaching Assistant in Department of Pharmaceutical Sciences (COP, UNMC) in 2018. Her research interests are biological evaluation of nanoformulations in vitro and in vivo, stem cell research, RNAi research, and investigating the interactions of myeloid immune cells with different stimuli such as SARS-CoV-2 and GM-CSF.

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Reversible Parkinsonism in a young man fusociated with severe sleep apnea

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Introduction: RLS atfects 10% of the population and is predominantly inherited. Acquired RLS is comorbid with PD in up to 50%. This comorbidity is poody'understood with RLS following motor manifestations, commonly in advanced disease, or attributed to treatment.

Methods: 78 patients with PD and RLS completed a survey addressing epidemiology, timing cf symptoms, comorbidities, and family history. Results were compared to 900 patients with primary RLS.

Results: In 41 (53%) PD preceded RLS and 33 (42y") RLS was antecedent. Patients with PD were 59% femalevs.T4o/ oinprimaryRLS. Meanage of RL Sonset was 62.5years with PD and 40.4 years wiihout. Mean age at diagnosis was 76.7 years in PD and 53.4 in primary RLS. 16 QA%) had RLS 10 or more years before PD. The remainder approximated a Gaussian distribution with 20% having RLS within 1 year of PD and only 9% more than 5 years after PD Growing pains (28 vs 50%), Migraines (43 vs 65%) and family history of RLS (18 vs 43%) were more common in primary RLS. These rates were not significantly different in PD paiients with antecedent or subsequent RLS including a subgroup analysis of the patients with RLS 10 or more years before PD.

Conclusion: RLS can precede the development of motor signs in PD by more than 10 years and may be a common premotor manifestation. Age at onset and presentation and absence of migraines, growing pains and FH of RLS may distinguish these patients from primary RLS.

Biography

David J Dickoff is a neurologist in Yonkers, New York and is affiliated with multiple hospitals in the area, including Mount Sinai Hospital and St. John's Riverside Hospital. He received his medical degree from Albany Medical College and has been in practice for more than 20 years

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Aneurysm arising at the origin of a Duplicated Middle Cerebral Artery

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A duplicated middle cerebral artery (DMCA) is a common anomaly. However, aneurysms arising from the origin of a DMCA are extremely rare. A 22-year-old female was admitted to our hospital with a World Federation of Neurosurgical Societies grade 2 subarachnoid haemorrhage. Four-vessel angiography revealed a DMCA and an aneurysm arising from the origin of this artery. The aneurysm was successfully treated by embolization and the patient was discharged 2 weeks later. Ruptured aneurysms arising from the origin of a DMCA can be successfully treated by embolization. These aneurysms are small and 3D-computed tomography reconstruction is mandatory to detect them. It is important to preserve the DMCA during the treatment procedure.

Biography

Jean Roch Alliez is a neurosurgeon practicing in the clinic clairval in Marseille. He completed his training at the Timone University Hospital, Hôpital Nord in Marseille and Hôpital Val de Grace in Paris. He has been practicing at Clairval since 2006 in the field of general spinal neurosurgery, neuro oncology and participates in the neurovascular pluridisciplinary activity within the establishment. Clinique Clairval is one of the most active neurosurgery centers in France. He visited a neurosurgical team in Houston in 2008 and in Montreal in 2021.

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CD271+ stem cell treatment of patients with Chronic Stroke

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Patients with chronic stroke have currently little hope for motor improvement towards regaining independent activities of daily living; stem cell treatments offer a new treatment option and needs to be developed. Patients with chronic stroke (more than 3 months prior to stem cell treatment, mean 21.2 months post stroke) were treated with CD271+ stem cells, 7 patients received autologous and 1 allogeneic cells from first degree relative; administration was intravenous in 1 and intrathecal in 7 patients. Each patient received a single treatment consisting of 2 5x106 cells/kg and they were followed up for up to 12 months. There were significant improvements in expressive aphasia (2/3 patients) spasticity (5/5, of which 2 were transient), and small improvements in motor function (2/8 patients). Although motor improvements were minor in our chronic stroke patients, improvements in aphasia and spasticity were significant and in the context of good safety we are advocating further administration and clinical studies of CD271+ stem cells not only in chronic stroke patients, but also for spastic paresis/plegia; a different, yet unexplored application is pulmonary emphysema.

Biography

Felician Stancioiu, MD is currently the principal investigator in a clinical study on the use of stem cells in autistic spectrum diseases, and also studying stem cell treatment of patients in neurovegetative state, stroke, ALS, spondylitis, spastic tetraparesis. He started working with hematopoietic stem cells in 1995-1997 worked at Stem Cell Sciences in New York, NY with Prof Niculae Ciobanu and is currently the Medical and Research Director at Fundatia Bio-Forum, Bucharest, Romania and has published original research in Endocrinology, Psycheneuroendocrinology and Neurology.

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Reelin alleviates pathological α-Synuclein aggregation and cell senescence in an *in vitro* model of Parkinson's Disease

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Statement of the Problem: Parkinson's disease (PD) is a neurodegenerative disorder caused by the gradual deterioration of midbrain dopaminergic (DA) neurons in the substantia nigra pars compacta. Changes in DA cells lead to tremor and rigidity, and induce a slow decline of the extrapyramidal motor system. Despite this, treatments for PD and its underlying pathogenesis remain understudied. Mesenchymal stem cells (MSCs) are multipotent cells that can differentiate into neuron-like cells, and they have been studied as part of potential therapy for PD. We questioned what the differences would be in molecular and cellular levels between the control and PD patient MSCs, and how to increase the survival rate of MSCs. Since PD is an age-related neurodegenerative disease associated with systemic problems, including inflammation, MSCs isolated from the abdominal adipose tissue were used in our cell model for PD to conduct gene expression profiling (GEP) investigation in this study.

Methods: Human adipose derived mesenchymal stem cells (MSCs) were obtained from a female volunteer, age of 68 as a control. An age matched female patient with PD, aged 68 years, who was not receiving any pharmacological treatment, was included in this study. For genome pathway analysis, DAVID software and KEGG pathways were selected. By DAVID software, our study found which pathways were down-regulated in PD cell.

Findings: Our results provide important data pertinent to research of the mechanisms underlying PD and potential treatment targets by transcriptome analysis in PD.

Conclusion: In this study, the GEP of MSCs on both PD cells and control group was analyzed. RELN was among ECM-receptor related genes whose expression is down-regulated in PD and hr-Reelin prevented PFF-induced α-Syn aggregation. A better understanding of Reelin functions and regulation in PD will be necessary to improve the prospects for successful treatment of PD.

Biography

Eunju Cho has her expertise in discovering potential therapeutic candidates to improve behavioral symptoms and to prevent exacerbating neuropathological features of Parkinson's disease (PD). She investigated the underlying mechanism of transient receptor potential vanilloid 1 (TRPV1) mediated therapeutic effects related to astrocyte responses in 1-methyl-4-phenylpyridinium (MPP+)-induced PD animal model during her M.S. thesis and she confirmed human relevance of altered Reelin gene and protein levels with neurodegenerative disease in PD patient-derived adipose stem cells during her Ph.D. course. Now she elucidated therapeutic effects and underlying mechanisms of Reelin with environmental enrichment in both cell model (Preformed fibrils) and transgenic mouse ((Prnp-SNCA*A53T)83Vle/J) model of PD. Based on her research, she has journal publications and two patents pending in South Korea regarding the Reelin protein in PD.

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The association of insulin resistance in CNS and Parkinson ' s disease

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Type 2 diabetes is a risk factor for many neurodegenerative diseases. Insulin receptor distributes wildly in brain including hypothalamus, hippocampus cerebellum, amygdale and cerebral cortex. Insulin signal contributes to many neuronal functions such as neuronal proliferation or synapse activation. Especially, Alzheimer's disease has been proposed as "Type 3 diabetes". Study found increased insulin resistance in Alzheimer's disease patient's brain as elevated phosphorylated serine 616 of insulin receptor substrate -1 (p-IRS-1 S616) in hippocampus neuron. Diabetes also increases the risk of Parkinson's disease (PD). The role of insulin signal in PD disease development is largely unclear. Clinical study found that PD patients with dementia (Parkinson's disease dementia, PDD) are two times more likely to have insulin resistance than the patients with PD without dementia. Insulin therapy through intranasal delivery also protects dopaminergic neuronal death in rat substantia nigra and alleviates motor deficits in a 6-OHDA induced PD rat model. In order to reveal the insulin signaling in neurons, neuron-derived extracellular vesicles (NDEVs) in blood provides a close information of insulin signal status in patients' neuron. We found that PD patients exerted significantly higher level of p-IRS-1 S312 in blood NDEVs than controls patients and patients with DM only. In addition, the levels of p-IRS-1 S312 in NDEVs was positively associated with the severity of tremor in PD patients after adjusting of age, sex, hemoglobin A1c, and body mass index (BMI). These findings suggested the association between dysfunctional insulin signaling pathway with PD. The role of altered p-IRS-1S312 in blood NDEVs as a segregating biomarker of PD required further cohort study to assess the association with the progression of PD.

Biography

Szu-Yi Chou is a associate professor, the PhD program for neural regenerative medicine. She started her career in Chang Gang University department of medical biotechnology and laboratory science, Taiwan in 1991. She got master in National Defense Medical Center, department and graduate Institute of Biology and Anatomy, Taiwan in 1998. She completed her PhD in the field of Neurodegenerative disease in National Defense Medical Center and post doctorate in Institute of Biomedical Science (IBMS), Taipei, Taiwan. Her research interests are Neuronal cell biology, Neurodegenerative disease animal model, Cell biology and molecular biology, Neuroendocrinology and Physiology – system physiology, circulation, and cardiovascular disease.

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Treatments for unruptured intracranial aneurysms

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Objectives: To analyze the risks and benefits of performing an interventional procedure (microsurgical clipping or endovascular embolization) compared to conservative treatment and to assess the risks and benefits of interventional treatments (microsurgical clipping vs. endovascular embolization) for unruptured cerebral aneurysms. This review examines evidence from randomized clinical trials addressing the risks of recurrent events and the risk of early intervention.

Methods: A search was performed in the Cochrane Stroke Review Group Trials and also in MEDLINE, EMBASE, LILACS and other databases from their respective creations until May 2020. There was no language restriction in the search. Colleagues were contacted to identify further unpublished studies. All complete and randomized studies comparing microsurgical clipping or endovascular embolization and conservative treatment and also complete randomized studies comparing microsurgical clipping and endovascular embolization for individuals with unruptured cerebral aneurysm were included. The authors individually selected studies for inclusion or exclusion, measuring the quality and risk of bias of the studies, and performing data extraction. An intention-to-treat analysis strategy was used.

Results: Only one randomized trial involving 136 participants comparing conservative treatment and endovascular embolization and one randomized trial comparing microsurgical clipping and endovascular embolization for individuals with unruptured cerebral aneurysms was identified. No statistically significant difference was found between the conservative treatment and endovascular embolization groups. New neurological deficits occurred more in surgically treated patients (16/65, 24.6%; 15.8% to 36.3%) vs 7/69 (10.1%; 5.0% to 19.5%); OR 2.87 (95% confidence interval (CI) 1.02 to 8.93), P = 0.038. Length of stay for more than five days was also longer in the microsurgical clipping group (30/65 (46.2%; 34.6% to 58.1%) vs 6/69 (8.7%; 4.0% to 17.7%); OR 8.85 (95% CI 3.22 to 28.59), P = 0.0001. After one year of clinical follow-up, one patient in each group died (48 patients underwent microsurgical clipping and 58 underwent endovascular embolization) and 1 patient in each group was disabled (mRS > 2). of very low evidence.

Conclusions: At the conclusion of this study, there was not enough good-quality evidence available from a randomized clinical trial to support conservative treatment or interventional treatment (microsurgical clipping and endovascular embolization) for individuals with unruptured cerebral aneurysm. Thus, additional randomized studies are needed to determine whether the intervention is better than conservative treatment and, if so, which intervention would be better and for which patients. Future studies should stratify participants by age, gender, aneurysm size and location (anterior or posterior circulation), degree of ischemia and length of stay.

Biography

Felipe Gomes de Barros Pontes has her expertise in neurosurgery and passion in improving the health and wellbeing. He does surgeries, teach and research both in hospital and education institutions.

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Regenerative capacity of bone marrow stem cells with or without superparamagnetic iron oxide nanoparticles after facial nerve degeneration: a narrative review

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Facial palsy can be defined as a kind of paralysis affecting facial muscles. It may occur due to trauma to the facial nerve, infections as herpes zoster, neoplastic lesions, or unknown cause. It may be also associated with metabolic and systemic diseases as hypertension, toxicity, amyloidosis, alcoholism, auto-immune diseases and diabetes mellitus. Mesenchymal stem cells are multipotent adult stromal cells that have many benefits as an evolving treatment modality. Bone marrow stem cells divide progressively in culture, and differentiate into neurons exclusively with use of a simple protocol. Most ongoing preclinical and clinical cell treatment modalities composed of local or systemic transplantation of stem or progenitor cells. In addition, they depend on the migration and retention of transplanted cells at insult areas. Nevertheless, one of the main obstacles against this modality is how to detect the fate and exact location of these cells inside the body, and how to maintain the cells at this specific site. Magnetic targeting systems, which depends on cells labelled by magnetic carriers, have been assessed as a more efficient technique for stem cell delivery to target sites. These systems depend on loading stem cells with magnetic nanoparticles and attracting them to the exact intended area within the body by placing an external magnetic field. Superparamagnetic iron oxide nanoparticles (SPIONs) have been introduced int the last few years as a rising applicant of nanoparticles in a vast variety of medical fields as magnetic separation, drug delivery, magnetic resonance imaging and magnetic hyperthermia. In addition, applications of SPIONs, as a site-specific drug carrier, diagnostic agent and stem cell delivery agent, receive most attention of researchers in that field.

Conclusion & Significance: Up-to-date information about Magnetic targeting of degenerated facial nerve by BMSCs labelled with SPIONs may suggest its capacity of better regeneration than injection of BMSCs alone.

Biography

DMD Noura Hasan has her expertise in evaluation and passion in improving the health and wellbeing. Her open and contextual evaluation model based on responsive constructivists creates new pathways for improving healthcare. She has built this model after years of experience in research, evaluation, teaching and administration in Faculty of Dentistry, Mansoura University.

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Natural plant products based therapeutics: a search for new generation of combination therapy and phytopharmaceuticals for Parkinson's disease

Sinjan Choudhary
University of Mumbai, India

α-Synuclein (α-Syn) is an intrinsically disordered protein expressed ubiquitously in various parts of nervous system and is involved in many biological processes like release of neurotransmitter and vesicular trafficking. But this protein is highly prone to aggregation even under physiological condition and leads to various neurodegenerative diseases like Parkinson's disease (PD). Most of the conventional drugs for the treatment of PD are synthetic in nature and are not fully efficient in preventing the progress or curing the disease. In addition, they are also coupled with several adverse side-effects. Plant based natural products are rich source of active components having diverse bioactivity. Natural products are expected to have high efficiency as well as less side effects and henceforth may offer alternative therapy for PD. Though their herbal preparations have long been used in the treatment of variety of diseases such as cancer, cardiovascular disorders, ophthalmic problems, liver dysfunction and many others, their potential against protein fibrillation is mostly unexplored. Many plant products such as safranal, algal sulfated polysachcharides, plant metaboilite like butein, diadzein, fisetin and scopoletin have been found effective against α-Syn fibrillation. Some of these molecules like diadzein and scopoletin are capable of crossing BBB and therefore can be considered as effective lead candidates for the development of drug molecules against PD. A comprehensive exploration of the effects of such plant derived bioactive compounds on α-Syn fibrillation will help in designing the appropriate interventions and also in development of new generation of phytopharmaceuticals, which can be used alone or in combination with other drugs aimed for Parkinson's disease.

Biography

Sinjan Choudhary is currently working as Assistant Professor in the Department of Chemistry, UM-DAE Centre for Excellence in Basic Sciences, Mumbai. She obtained her M.Sc. in Biotechnology (2008) from Jawaharlal Nehru University, New Delhi and a Ph.D. in Biophysical Chemistry (2012) from Indian Institute of Technology Bombay, Mumbai. He has performed fundamental work in Biophysical characterization of protein-solvent and drug-protein interactions and protein folding intermediates using combination of spectroscopy and calorimetry during her Ph.D. Subsequently, she joined UM-DAE Centre for Excellence in Basic Sciences, Mumbai for her postdoctoral studies (2013-2015). As a postdoctoral fellow she was involved in structural characterization of ribosomal proteins from different parasites using different biophysical techniques. She started independent research work on 'Inhibition of protein fibrillation related diseases small molecules' which was supported by DST-SERB Early Career Research Award. Her research work has been published in various reputed international journals. She has also been inducted as Editorial Board Member of Journal of Chemical Thermodynamics and Guest Editor of International Journal of Food Science and Technology titled "Functional foods and bioactive compounds in the management of neurodegenerative diseases". She is recipient of various awards such as "Professor Shantilal Oswal Young Scientist Award" and "Giauque Memorial Award" in recognition of the research work. She has also recently initiated research on prevention of Malaria with the support of DST-SERB Core Research Grant. Dr. Choudhary's current research group is involved in small molecules and plant products based therapeutics for neurodegenerative and infectious diseases. She has published around 40 research publications in various reputed scientific journals.

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Clinical characteristics and Neurophysiology features of Amyotrophic Lateral Sclerosis patients at Sanglah Hospital Denpasar

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Background: Amyotrophic lateral sclerosis (ALS) is a one of motor neurons disease. The Incidents in Europe are 2.6 per 100,000 people per year and in the United States, more than 5,600 are diagnosed each year. The death was reportedly 2 per 100,000 people per year. In Sanglah Hospital there are no study that described the characteristics clinical and neurophysiology of ALS at Sanglah Hospital.

Objective: To find the characteristics of ALS based on clinical and neurophysiology of ALS at Sanglah Hospital in terms of demography, clinical, Nerve Conduction Studies (NCS) and Electromyography (EMG).

Methods: Retrospective descriptive study using medical records of patients in neurology polyclinic at Sanglah Hospital from January until December, 2018. Results. From 14 ALS patients with average age of 47 years old, men and women same amount, high school 71.4%, unemployed 50 %, and married 92.8%. Symptoms first appeared with an average age of 42 years with complaints of lower limb weakness 64.3%. The diagnosis of ALS with the symptom UMN and LMN on bulbar and 2 spinal region 71.4%, and symptom with the UMN and LMN on 3 spinal region 28.6%.

Results: Results of motor and sensory NCS were normal, type axional and mixed neuropathy. Characteristics of EMG were PSW +4, fibrillation +4, MUAP: high amplitude (giant potential), widened duration, polyphasic phase, incomplete IP recruitment in all patients (100%) although in different muscles of the examined patient.

Conclusions: Characteristics from 14 patients ALS in 2018 at Sanglah Hospital indicate that patients have a good prognosis.

Biography

Ni Made Dwita Pratiwi is a talented neurologist staff at neurology department of Sanglah National Public Hospital who has interests in neurophysiology, especially electroneurography. She experienced neuromuscular cases with broad complexity level and sometimes a unique / rare case. She also is a lecturer in Udayana University and actively mentoring co-assisstants and residents, so her knowledge are always fresh and updated. Indeed, she is a good place to have a discussion with for her line of interest.

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Understanding the conformational dynamics of intrinsically disordered protein α-Synuclein in urea and Trimethylamine oxide (TMAO)

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Intracellular inclusion of aggregated and misfolded α-synuclein is the major cause of Parkinson's disease (PD) that leads to the degradation of dopaminergic neurons in the brain cells. α-synuclein aggregates are found in Lewy bodies which is the characteristics of PD. Understanding the mechanism of α-synuclein aggregation will facilitate the problem of dealing with neurodegenerative diseases in general and that of PD in particular. In our study, the mechanism of aggregates formation and behaviour of α-synuclein in presence of denaturing osmolyte 'urea' and protecting osmolyte 'TMAO' has been investigated through molecular dynamic (MD) simulation at various concentrations. Behaviour of α−synuclein in water at different temperature has also been investigated. Both of these osmolytes have contrasting effect on α−synuclein. Urea being a denaturing osmolyte, leads to extended conformation of protein by interacting more with α−synuclein through hydrogen bonds formation however; compact conformation has been adopted by protein in presence of TMAO. Along with the experimentally know region 61-95, some other regions of α−synuclein have also been identified which have the propensity to form an aggregates. Dynamics of water molecules has also been investigated and is correlated with the aggregation property of α-synuclein.

Biography

Ishrat Jahan is working as a postdoctoral fellow at Department of Chemistry, Indian Institute of Technology Delhi, India. Currently, working on understanding the aggregation behaviour of alpha-synuclein in silico and *in vitro*.

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