LATE-BREAKING ABSTRACTS

International Parkinson and Movement Disorder Society
Asian & Oceanian Section

MOVEMENT DISORDERS SOCIETY OF INDIA 2014

8th Asian and Oceanian Parkinson's Disease and Movement Disorders Congress

MARCH 17-19, 2023

Kolkata, INDIA

8th Asian and Oceanian Parkinson's Disease and Movement Disorders Congress®

2023 Late-Breaking Abstracts

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LBA-6: Mesenchymal stem cell-derived exosomes inhibit alpha-synuclein aggregation
Farhang Aliakbari, Kimiya Marzokian, Soha Parsafar, Hamdam Hourfar, Narges Nasrollahi Boroujeni, Zahra Nayeri, Mohammad Raeiji, Paniz Mirsadeghi, Maryam Malakouti-Nejad, Dina Morshedi

LBA-1: Unsupervised clustering of whole-brain dopamine transporter binding pattern predicts overall survival in multiple system atrophy

Jung Hwan Shin, Youn-koo Kang, Hongyoon Choi, Han-Joon Kim, Beomseok Jeon

Objective: We aim to develop an imaging biomarker based on whole-brain DAT binding pattern and its correlation with clinical prognosis in MSA.

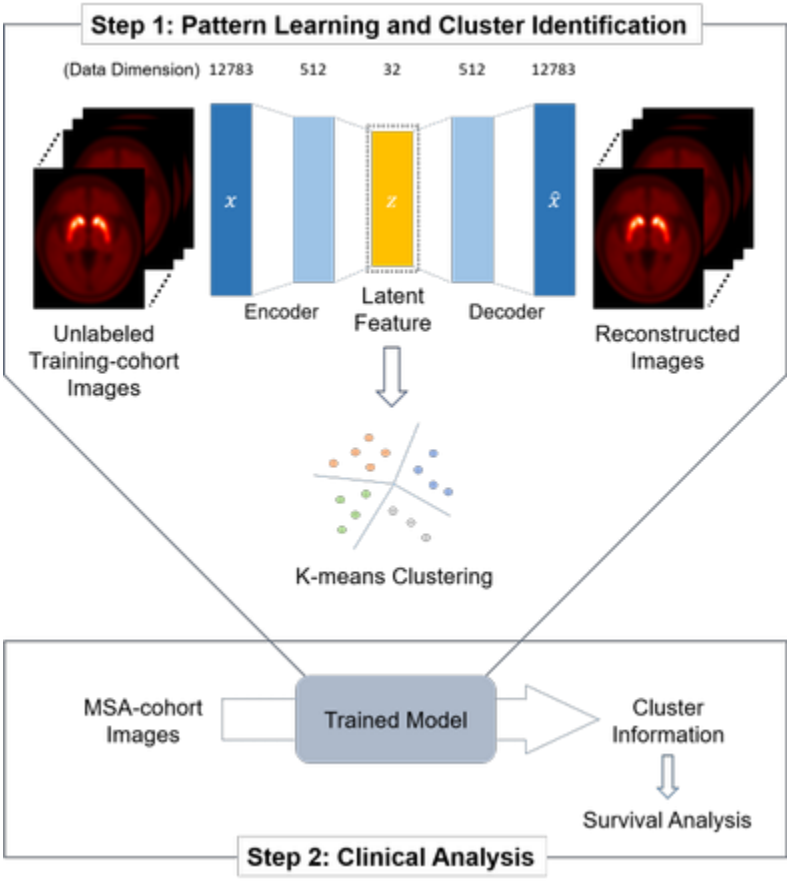
Background: Multiple system atrophy (MSA) is an atypical parkinsonian syndrome that presents with parkinsonism, cerebellar syndrome and autonomic function impairment. Patients with MSA show a rapidly progressive clinical course with a median survival duration from disease onset ranging from 6~10 years. Also, MSA is known for the multi-systematic involvement of the central nervous system. From autopsy reports, MSA show characteristic glial cytoplasmic inclusions (GCIs) and resulting neurodegeneration in striatonigral, olivopontocerebellar and nuclei of the brainstem including locus ceruleus, raphe nucleus and dorsal vagal nucleus. Within the overall rapid disease course, the clinical outcome of individual MSA patients is variable. In a meta-analysis of survival in pathologically proven MSA, the survival duration ranged from 0.5 to 24 years. This variability suggests that there might be a subgroup of MSA patients that presents with a different outcome. Thus, identifying the objective biomarker that can cluster a subgroup of MSA based on clinical prognosis is warranted for disease monitoring and future clinical trials. There have been several clinical factors that are associated with shorter survival including older age of onset, gender, early autonomic symptoms and absent levodopa responses. However, objective biomarker that reflects brain-wide neurodegeneration pattern that could predict the clinical outcome of MSA has not been clearly understood.

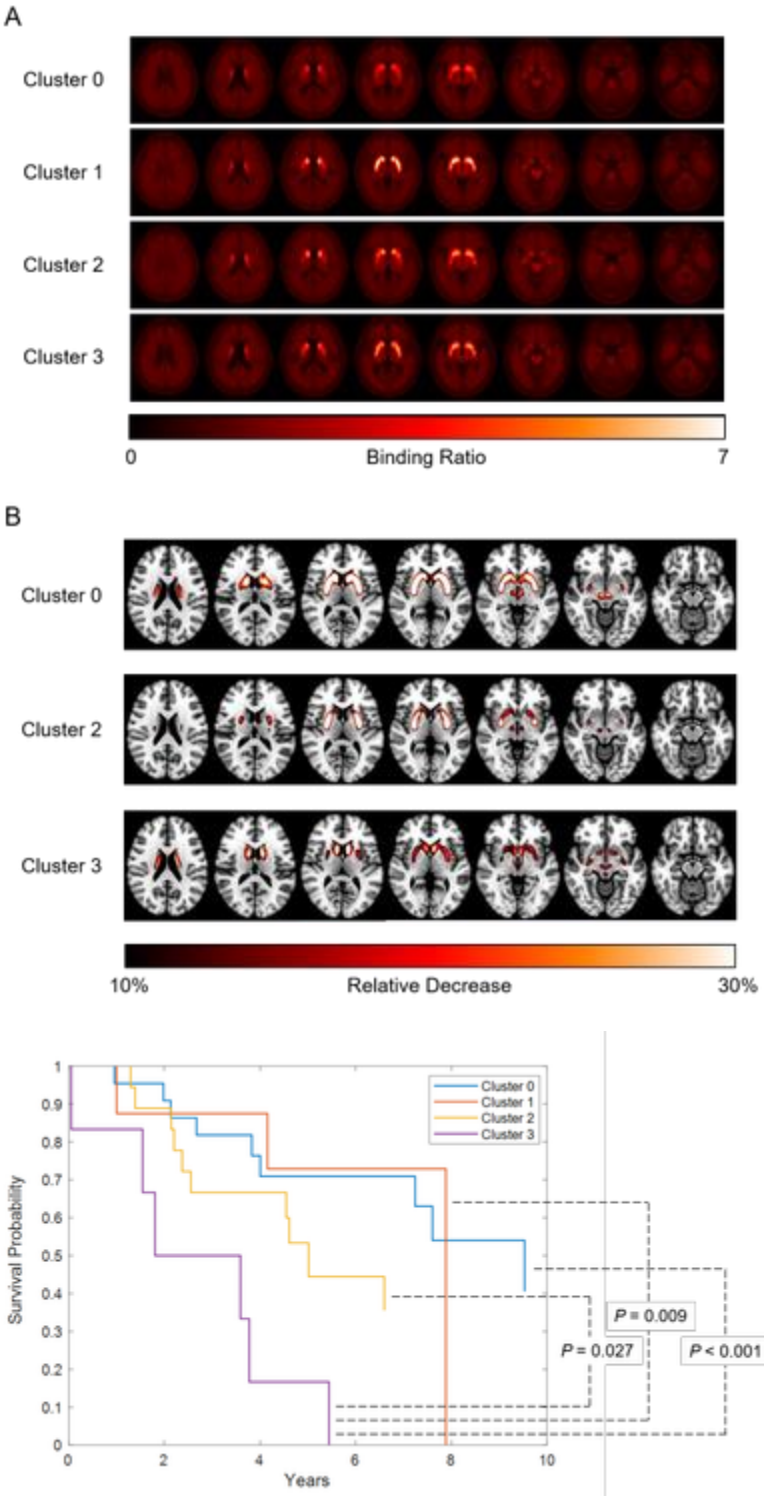
Methods: The study consists of two steps. In the first step, an unsupervised learning-based deep learning model for clustering of FP-CIT PET was designed by patients who underwent FP-CIT PET from January 2015 to June 2018 (n = 813). All FP-CIT PET images from the training cohort were learned and classified by an autoencoder-based unsupervised clustering model without diagnostic labeling. PET images were analyzed after being transformed to binding ratio values with the occipital cortex as a reference region. In the second step, we applied the pre-defined clusters from unsupervised learning to clinically probable MSA who underwent FP-CIT PET (n=54) from 2009 to 2018 (n = 54). We collected the survival information of enrolled MSA as of August 2020 from the National Health Information Database in South Korea. Cluster information produced by the model was tested for the predictive value of overall survival in MSA.

Results: The unsupervised clustering model successfully classified FP-CIT PET images into four clusters with discrete spatial image patterns – cluster 0 with whole striatal involvement, cluster 1 with intact binding, cluster 2 with posterior putaminal involvement and cluster 3 with caudate and raphe involvement. In survival analysis in the MSA cohort, 28 patients (52%) died 3.6 ± 2.4 years after PET imaging. Median overall survival was 6.6 years (95% CI 4.5 – 9.5 years). On the Kaplan-Meier curve, the shortest overall survival was observed in cluster 3, followed by clusters 2, 1 and 0 (p = 0.002 by log-rank test). Among clinical features and DAT imaging factors, cluster

information and brainstem binding ratio were independent predictors for overall survival (p = 0.001 and 0.017 by Cox proportional hazard regression analysis).

Conclusion: We propose an imaging biomarker produced by unsupervised clustering of whole brain DAT binding pattern. The clusters within MSA showed significant prognostic value on overall survival prediction in MSA, which warrants further model refinement and validation in large cohorts for future clinical application.





LBA-2: Neuroprotective role of serotonin in Parkinson's disease neuronal cell model

Archana Dwivedi, Mohammad Faruq, Anand Kumar, Deepika Joshi

Objective: To study the neuroprotective role of serotonin in Parkinson’s Disease using a neuronal cell model.

Background: Current therapy for Parkinson's disease (PD) is symptomatic or based on exogenous supplementation of DA with levodopa, but in long term, it can lead to the development of dyskinesia. As a safer anti-PD therapy, new pharmacological approaches are now focusing on other neurotransmitter systems. Serotonin (5-HT) is particularly interesting. In vitro experiment shows that 5- HT can inhibit α-syn amyloidogenesis and 5-HIAL, an aldehyde of serotonin, can oligomerize α-syn, while the computational model shows that at the very early stage of the disease, an increase in 5- HT concentration could partially recover DA release. Interactions between serotonin and dopamine have been investigated for decades, but the role of serotonin as a neuroprotective molecule for dopaminergic neurons in the case of PD is still not done. It seems 5-HT might have an important role in the neuroprotection of DA neurons. So, here we are trying to study the effect of serotonin on the neuronal cell model of PD.

Methods: Establishment of in vitro human neuronal cell model for PD, using i) Human neuroblastoma SH-SY-5Y cells cultured in 10% DMEM media and differentiated for 7 days in 1% FBS DMEM media and 10 µM retinoic acid, with media replaced every 2 days and ii) wild type and A53T mutant α-syn protein expressed from pET-21a vector used to generate Pre-Formed Fibrils (PFFs) of α-syn. The differentiated cells were treated with α-syn PFFs to generate a PD model, and these were further subjected to various concentrations of 5-HT. Neuroprotective effect studied by cytotoxicity analysis by MTT assay or using biochemical techniques such as immunocytochemistry and immunoblot analysis etc. Statistical analysis was done to interpret the results.

Results: The α-synuclein preformed fibrils seeded SH-SY-5Y cells are good model to study PD. Moreover, treatment of neurons with 5-HT before giving them α-syn PFF milieu increases the percentage cell viability as compared to treatment of cells with α-syn PFF alone.

Conclusion: We have worked towards the identification of a novel, physiologically relevant interaction between DA, α-syn, and 5-HT in PD. Our result shows that treating DA neuronal cells with 5-HT is neuroprotective and hence could be utilized as a new therapeutic approach for PD.

LBA-3: The VEP, BAER, and SSEP cut-off values for postural instability in Idiopathic Parkinson's disease and Parkinson Plus Syndrome

Joydeep Mukherjee, Amar-Kumar Misra, Manoj Roy, Manamita Mandal

Objective: Postural stability is of utmost importance for reducing the morbidity and mortality of parkinsonism patients. Sensory inputs from vision, hearing and limb sensations play an important role in maintaining balance. Though parkinsonism predominantly involves the extrapyramidal motor system, more and more research is available to show additional significant non-motor involvement. Our objective is to find out the role of disturbed sensory inputs in the postural instability of parkinsonism patients. So, we tried to establish cut-off values of VEP, BAER, and SSEP for postural instability in them.

Background: Postural instability causes recurrent falls in parkinsonism patients and is multifactorial. Visual evoked potential (VEP), brainstem auditory evoked potential (BAER), and somatosensory evoked potential (SSEP) denotes the functional integrity of many white matter tracts which provide continuous sensory inputs to maintain stability. If the evoked potentials could classify for postural instability, it would be easier to monitor and reduce morbidity and mortality.

Methods: Fifty non-consecutive patients of idiopathic Parkinson's disease (IPD) and fifty Parkinson plus syndrome (PD_plus) were diagnosed by validated clinical criteria and enrolled in NRS medical college & hospital from September 2020 to August 2022. Modified Hoehn and Yahr scale stage 0 to 2.5 was without postural instability, and stage 3 to 5 was with postural instability. VEP, BAER, and SSEP were recorded by using Nihon Kohden Neuro pack II plus. SPSS version 26 was used to make ROC curves and denote significant results using $p < 0.05$.

Results: The latency of bilateral VEP N75, P100, and right N145 has significant cut-off values in IPD patients for postural instability. At the same time, only N75 latency and N75-P100 amplitude were significantly classified in the PD_plus group for postural stability. IPD patients also had significant cut-off values in BAER wave II, II, IV, and V latency and inter-peak latency of I-III and I-V (more on the left side) for postural stability. PD_plus patients' bilateral BAER wave I latency significantly classifies the patients with and without postural instability. The IPD group had significant classifiers in bilateral N9, N13, and N20 latencies for postural instability. N13 and N20 latencies in SSEP classified the PD_plus patients significantly according to postural instability. Subgroup analysis also showed remarkable findings.

Conclusion: Various VEP, BAER, and SSEP cut-off values can be used to determine the probability of postural instability with certain sensitivity and specificity in IPD and PD_plus patients.

LBA-4: The genetic drivers of young- and early-onset Parkinson's Disease in India

Shan Andrews, Prashanth Kukkle, Ramesh Menon, Thenral Geetha, Vinay Goyal, Rukmini Mridula Kandadai, Rupam Borgohain, Adreesh Mukherjee, Pettarusp Wadia, Ravi Yadav, Soaham Desai, Niraj Kumar, Deepika Joshi, Sakthivel Murugan, Atanu Biswas, Pramod Pal, Merina Oliver, Sandhya Nair, Anbu Kayalvizhi, Udita Mahadevia, Susinder Sundaram, Manjari Deshmukh, Akshi Bassi, Charugulla Sandeep, Nitin Mandloi, Uday Muthane, Shymal Das, Andrew Peterson, Thomas Snadmann, Ravi Gupta, Vedam Ramprasad

Objective: This study sought to identify the genetic drivers of young- and early-onset Parkinson's Disease in India.

Background: Recent studies have advanced our understanding of the genetic drivers of Parkinson's Disease (PD). Rare variants in more than 20 genes are generally accepted to be causal for PD, and the latest PD GWAS study identified 90 independent risk loci. However, there remains a gap in our understanding of PD genetics outside of the European populations in

which the vast majority of these findings occurred. Limited, small-scale studies in East and South Asians have demonstrated that distinct risk factors may exist in these populations, emphasizing the need to characterize the genetic factors driving PD in these groups directly.

Methods: PD subjects with age of onset ≤ 50 years (encompassing juvenile, young, or early-onset PD) were recruited from 10 specialty movement disorder centers across India over a 2-year period. PD cases (N = 675) were genetically profiled via the South Asian Research Genotyping Array (SARGAM) and WES at 60x average coverage. Ancestry-matched controls (N = 1363) were derived from the reference WGS GenomeAsia 100K population, Phase 2 (GAsPh2). GWAS of common variants (MAF > 5%) for PD diagnosis and symptom age of onset was performed using merged SARGAM PD case data and GAsPh2 WGS control data. WES data was also used to identify PD cases harboring pathogenic/likely pathogenic variants in 21 previously identified monogenic PD genes. Finally, PD case WES data was merged with WGS control data, adjusted for platform and coverage differences, and used to quantify differential burden of rare (MAF < 1%) and predicted deleterious (per PolyPhen2 and CADD) variants.
Results: Common variant GWAS of PD diagnosis yielded a GW significant result (lead SNP p-value = 4.1E-11) in a region containing the canonical PD gene SNCA. This signal strongly colocalized (posterior probability = 1) with SNCA region signal from European PD GWAS. Pathogenic variants, including homozygous PRKN deletions, were identified in 8% of PD cases. PD cases with pathogenic mutations in PD genes exhibited, on average, lower PD polygenic risk scores than PD cases lacking PD gene mutations. Top-ranked genes from WES-based gene burden studies of LoF and deleterious variants included BSN and AMPD1, which have previously been implicated in synaptic function and purine metabolism, respectively. However, no genes surpassed multiple testing correction, owing to the limited statistical power conferred by this cohort.

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Conclusion: This study constitutes the largest genetic investigation of PD and first demonstration of SNCA association with PD in an Indian population to date. Ongoing work will expand this cohort by an additional 1,000 PD cases, enabling improved statistical power to detect PD genes in this understudied group.

LBA-5: Using nanoliposome to pass oleuropein through the blood-brain barrier

Dina Morshedi, Farhang Aliakbari, Narges Nasrollahi Boroujeni, Soha Parsafar, Zahra Nayeri, Hamdam Hourfar, Kimya Marzokian, Mohammad Raeiji, Paniz Mirsadeghi, Maryam Malakouti-Nejad

Objective: The aim of this study is to evaluate the potential of nanoliposome as a carrier to pass oleuropein as a potent small molecule against alpha-synuclein aggregation through the blood brain barrier (BBB).

Background: The blood-brain barrier (BBB) is a membrane layer of cerebral capillary endothelial cells with strong cell-to-cell contacts that maintains the central nervous system (CNS) homeostasis. It also protects neurons against agents in the systemic circulation and prevents pathogens from entering the brain. BBB damage may occur during various brain disorders including neurodegenerative diseases. Although many drugs have been designed to combat CNS problems, many of them cannot cross BBB, and therefore, finding the way to deliver them into the brain is one of the pharmaceutical objectives especially in neurodegenerative diseases (ND). Oleuropein is a small molecule which has a proper potential to treat protein aggregation-related ND including Parkinson's disease. Due to short-live nature of oleuropein in physiological condition, its effectiveness decreases from the time of administration until it reaches the brain.

Methods: Here we formulated nanoliposome-incorporated oleuropein (NLP-Oleu) using thin film evaporation an then hydration to assess its efficiency to pass through BBB. We used zwitterionic phospholipid for the formulation of nanoliposome and further decorated it with transferrin.

Results: Nanoliposome stabilizes oleuropein and solves its hydrophobicity shortcoming. Transferrin further helps nanoliposomes to pass oleuropein through the BBB. We fabricated an in vitro model of the BBB using hCMEC/D3 cells. NLP-Oleu caused more transfer of oleuropein from the BBB than free oleuropein.

Conclusion: These findings support the efficacy of nanoliposomes decorated with transferrin as a carrier to treat neurodegenerative disease.

LBA-6: Mesenchymal stem cell-derived exosomes inhibit alpha-synuclein aggregation

Farhang Aliakbari, Kimiya Marzokian, Soha Parsafar, Hamdam Hourfar, Narges Nasrollahi Boroujeni, Zahra Nayeri, Mohammad Raeiji, Paniz Mirsadeghi, Maryam Malakouti-Nejad, Dina Morshedi

Objective: The aim of this study is to assess the potential of mesenchymal stem cell-derived exosome to inhibit the fibrillation of alpha-synuclein (αSN).

Background: The aggregated species of alpha-synuclein (αSN) protein lead to the death of dopaminergic neurons and the pathology of Parkinson's disease (PD). Consequently, prevention

of αSN fibrillation can be an appropriate treatment for PD. Exosomes are a group of extracellular vesicles originated from multivesicular endosomes containing various macromolecules, the most important of which are non-coding RNA, proteins, and lipid cargos, which play special roles in the regulation of differentiation, activity, division, and function of recipient cells.

Methods: In this study, mesenchymal stem cells were extracted from human umbilical cord (hUC MSCs) using explant culture, and then their exosomes were isolated and purified. The potential of the purified exosomes to inhibit αSN fibrillation were then assessed using ThT fluorescence intensity and the in silico method.

Results: Results indicated that hUC MSCs-derived exosomes interacted to αSN leading to inhibit the fibrillation resulting in reduction of the end point product. These exosomes further affected on the secondary nucleation pathway.

Conclusion: These findings shed light on the therapeutic properties of exosomes as cell free treatment tool against αSN aggregates and their potential in combat of PD.