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LBA-1: Clinical utility of nigrosome-1 imaging in the differential diagnosis of sporadic adult-onset ataxias

D. Park, J. Choi, Y-S. An, J. Yoon (South Korea)

Objective: In this study, we investigated the clinical utility of nigrosome-1 susceptibility map-weighted imaging (SMWI) by 3T-MRI in assessing sporadic adult-onset cerebellar ataxia.

Background: Cerebellar ataxias are a heterogeneous group of disorders of genetic or non-genetic origin. It is often challenging to differentiate multiple system atrophy of cerebellar type (MSA-C) from other genetic or idiopathic late-onset cerebellar ataxias (ILOCA) in sporadic cases. Although clinical parkinsonism can support the diagnosis of MSA-C, it may not be evident in the earlier stage of the disease. Moreover, dopamine transporter (DaT) imaging may not be readily available and may cause unnecessary radiation exposure to some patients.

Method: We retrospectively reviewed the patients diagnosed with cerebellar ataxia at Ajou University hospital from December 2016 to February 2021, and those who had undergone both 18F-FP-CIT PET and nigrosome-1 MRI were selected. MSA-C was diagnosed based on the clinical criteria after more than one year of the follow-up period. “Swallow tail sign” in SMWI and putaminal atrophy were visually assessed by an experienced neuroradiologist. We assessed the diagnostic performance of initial nigrosome-1 imaging in differentiating MSA-C from other ataxias, compared with putaminal atrophy or striatal DaT availability.

Results: Among 39 patients reviewed, 32 patients were ultimately diagnosed with possible or probable MSA-C, whereas seven patients were diagnosed with either genetic ataxia or ILOCA. Putaminal atrophy was observed in 13 patients, and it had a sensitivity of 40.6% and specificity of 100% in the diagnosis of MSA-C. On the other hand, the swallow tail sign in nigrosome-1 MRI was observed in 29 patients, and it had a sensitivity of 84.4% and specificity of 71.4% in differentiating MSA-C from other ataxias, which was comparable to DaT imaging (sensitivity 81.3% and specificity 100%). Loss of hyperintensity in nigrosome-1 was consistent with DaT loss except for 3 cases, among which one was later diagnosed with MSA-C.

Conclusion: In differentiating MSA-C from other ataxias, nigrosome-1 MRI has superior sensitivity to putaminal atrophy, and its diagnostic performance is comparable with DaT imaging. Nigrosome-1 MRI can be a proper screening method in initial assessments of sporadic adult-onset ataxias.

LBA-2: Long-term clinical outcomes of thalamic deep brain stimulation in Tourette Syndrome

C. Hennen, J. Baldermann, S. Lopes Alves, T. Schüller, V. Visser-Vandewalle, J. Kuhn, M. Barbe, D. Huys (Germany)

Objective: To investigate long-term outcomes of deep brain stimulation (DBS) for Tourette Syndrome (TS), considering tic reduction as well as quality of life and patients’ satisfaction with treatment response.
Background: DBS is an evolving therapy for severely affected treatment-refractory patients with TS. Research on thalamic DBS has indicated the efficacy in tic reduction. However, case numbers remain limited, and most studies reported short-term outcomes. Assessing long-term follow-up data of clinical outcomes, especially considering psychosocial functioning and quality of life, is essential to estimate reliable risk-benefit ratios of the procedure.

Method: We conducted a longitudinal monocentric study including 16 patients who underwent DBS surgery to the medial thalamus between 2008 and 2016 (n= 14 bilateral, n= 2 unilateral). Yale Global Tic Severity Scale (YGTSS) scores, questionnaires focusing on psychosocial functioning (Global Assessment of Functioning Scale (GAF)) and quality of life (Gilles de la Tourette Syndrome – Quality of Life Scale (GTS-QoL)) as well as data on adverse events were reported preoperatively, one year after DBS surgery and at the latest possible follow-up (5.9 ± 2.7 years). In addition, patients were asked about their satisfaction with treatment effects and if they would retrospectively choose DBS surgery again.

Results: At the latest follow-up, stimulation was still active in 15 of 16 patients. Mean YGTSS total scores of these patients (n=15) improved significantly (p<0.001) from 77.13 ± 18.89 at baseline to 37.0 ± 28.91 one year after DBS surgery and 36.0 ± 27.08 at long-term follow up. Effects on YGTSS motor tic subscores were less pronounced than effects on vocal tic and impairment subscores. Mean GAF scores (n = 12) improved by 30 %, mean GTS-QoL total scores (n= 7) by 46 % from baseline to long-term follow-up. Subjectively, patients rated tic severity at long-term follow-up compared to baseline as 62 % lower (n=14). Of all 16 patients, 13 patients (81 %) stated that their expectations were fulfilled, and 15 patients (94 %) responded that they would retrospectively choose DBS surgery again. Most common stimulation-related side-effects were transient paresthesia and dizziness, present in 44 % and 38% of the cases.

Conclusion: In our cohort of severely affected TS patients, DBS effectively reduced tic severity and improved patients’ quality of life sustainably within a mean follow-up time of 6 years.

Disclosure: JCB and VVV are funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) (Project-ID 431549029 – SFB 1451).

LBA-3: Subanesthetic infusion of ketamine produces long-term reduction in levodopa-induced dyskinesia

T. Falk, SS. Richards, MJ. Bartlett, AE. Lind, C. Liu, CP. Hsu, ML. Heien, SJ. Sherman (USA)

Objective: An open-label, dose-finding Phase I/II clinical trial was conducted to test safety and tolerability of low-dose ketamine infusion to treat levodopa-induced dyskinesia (LID), and to find an effective dose-range suitable for outpatient use.

Background: Low-dose ketamine infusions are effective therapy for depression and chronic pain. Our prior preclinical and case report data [1-3] suggest that low-dose ketamine treatment has short-term antiparkinsonian activity and importantly can reduce existing LID long-term (≥3 mo) after an initial 10-hour total treatment.

Method: Two 5-hour low-dose ketamine infusions were given within a one-week period. Measured outcomes included: reduction of dyskinesia, captured with UDysRS (Unified Dyskinesia Rating Scale), and effects on parkinsonian symptoms, captured with UPDRS (Unified Parkinson's Disease Rating Scale). Statistics: linear mixed effects models. Subject diaries of on/off symptoms were collected. Plasma samples were collected for pharmacokinetic analysis of ketamine and metabolites.

Results: Analyses of the dose-finding study, show safety and tolerability in a population of subjects with moderate to advanced PD, and indicate possible efficacy with a large effect size that warrants further study. We screened 13 subjects: 3 were screen failures, 10 enrolled in the study, 1 did not complete the infusion due to nausea, 9 had complete infusions. The target infusion rate was 0.30 mg/kg/hr. The maximum tolerated infusion rate ranged from 0.20-0.30 mg/kg/hr. The side effects that prompted reduction of infusion rate were mostly discomfort due to dissociation or hypertension. No adverse events occurred post-infusion. UDysRS: 51% reduction from baseline during Infusion 2 (p=0.003), 49% at 3-week (p=0.006) and 41% at 3-month (p=0.011) post-ketamine. UPDRS: 27% reduction during Infusion 2 (p=0.057), 28% at 3-weeks (p=0.026) and 5% at 3-months (p=0.258). Analyses of the patient diaries and the pharmacokinetic data are ongoing.

Conclusion: Our results provide further support for the repurposing of sub-anesthetic ketamine for individuals with LID. A multi-center, double-blind, placebo-controlled Phase II/III trial, with midazolam as an active-placebo, is planned to start in 2022.

Disclosure: Declaration of Competing Interest: SJS and TF have a pending patent application for the use of ketamine as a novel treatment for levodopa-induced dyskinesia associated with Parkinson’s disease, that has been licensed to PharmaTher Inc.

LBA-4: Timed Up & Go - can it measure gait?

N. Eren, Z. Yekutieli (Israel)

Objective: Present the limitation of the standard 3m TUG for gait assessment, and suggest a way to enhance it.

Background: Timed-up-and-go (TUG) is a general physical performance test used to assess mobility, balance and locomotor performance in elderly people in general, and patients who suffer from movement disorders in particular. With balance disturbances. More specifically, it assesses the ability to perform sequential motor tasks relative to walking and turning (Schoppen, Boonstra, Groothoff, de Vries, Goeken, & Eisma, 1999; Morris, Morris, & Iansek, 2001). Developed by Mathias, Nayak, and Issacs in 1986, TUG has not changed since, with the main outcome of the test being the completion time (CT).

Mon4t has developed a smartphone-based app that allows, among other motor assessment, a digital recording of the TUG test. The app test was extensively used since it was released which allowed data...
collection of many subjects. When data was analyzed, we noticed that it is virtually impossible to evaluate the subject’s gait and dynamic balance during TUG, not only because the human rater lacks the capability to measure these factors, but also because the walking distance in the TUG test is too short to allow any normal steps. As 3m TUGs are currently the standard, and their CT as a standard output, we wanted to check whether we can slightly extend the length of the TUG test, gain valid gait data, while still predict the 3m completion time, thus being aligned with the standard.

Method: We have conducted TUG tests for 240 PD patients, each conducting two 3m TUGs and two 5m TUGs. Using the data derived from Mon4t app, each segment of the TUG test was separated (stand up, walk away, rotation, walk back, sit down), steps were analyzed, gait sway was analyzed, and a model was created to predict the 3m CT from the 5m CT. This prediction was then compared to the actual 3m CT obtained by the same patient.

Results: Using the data derived from Mon4t app, each segment of the four TUG tests conducted by the PD patients (two 3m and two 5m sessions) was separated into the different TUG segments - stand up, walk away, rotation, walk back, sit down. The patient steps were analyzed, gait sway was analyzed, and a model was created to predict the 3m CT from the 5m CT. This prediction was then compared to the actual 3m CT obtained by the same patient.

Computing the 3m CT from the 5m CT resulted with correlation coefficient of 0.9, p<<0.01

Using the Kolmogorov-Smirnov test, we demonstrated that the prediction error falls within the within test delta (between the two 3m repeats)

Conclusion: While 3m TUG is the standard of evaluation for many years, with Completion Time being a common (and so far, only) quantitative result of the test, a 3m TUG does not allow any normal walking pattern, and thus cannot be properly used to evaluate gait, a key factor in assessment of movement disorders. Performing a 5m TUG test offers sufficient walking steps and, by using Mon4t app, gait can be captured and analyzed, thus offering valuable information. As 3m TUG CT is currently a common standard, used for falling risk assessment and more, we offer a model that allows us to calculate the 3m TUG CT, from the 5m TUG. Thus, in one test, one can obtain both proper gait analysis, and the 3m CT standard. With enough 5m TUG tests conducted, that can ultimately become the standard of assessment, with 5m CT used.
LBA-5: Association between Insulin-Like Growth Factor-1 and Social Cognition in Huntington's Disease

E. Cubo, S. Horta, C. Gil, F. Sampedro, C. Collazo, E. Alonso, E. Riñones (Spain)

Objective: To investigate the hypothalamic function and its association with social cognition and other non-motor symptoms and brain structure in Huntington's disease.

Background: Dysfunction of the hypothalamus and the limbic system has been associated with the development of non-motor symptoms in Huntington's disease.

Method: This was a cross-sectional, observational, case-control study. We assessed apathy [Apathy Evaluation Scale-Clinician], anxiety, depression, and irritability [Hospital Anxiety and Depression Scale-Snaith Irritability scale], social cognition [Ekman 60 faces test], motor symptoms (Unified Huntington Disease Rating Scale), and functionality with the Total Functional Capacity scale. We compared oxytocin, vasopressin, corticotropic, somatotropic, gonadotropic, thyrotropic, and lactotropic axes between Huntington's disease patients and controls. The association of hypothalamic function with brain structure was analyzed using multivariate regression analysis.
Results: We included 22 patients with Huntington's disease, 41% males, 59% females, mean age of 58.09 + 9.72, median Total Functional Capacity score of 11.00 (9.75;13.00), and 19 age/gender matched controls. Compared to controls, Huntington's disease patients had greater social cognition impairment (p<0.001), and apathy (p<0.001). In the multivariate regression analysis, Ekman total scores were negatively associated with Huntington's disease [β=-12.25, 95% CI:16.51; -7.98, p<0.001], intake of antidopaminergic drugs [β=-5.91, 95% CI: -11.11; -0.11, p=0.02], and positively associated with insulin-like growth factor-1 levels (IGF-1) [β=0.06, 95% CI:0.001;0.12, p=0.04]. In Huntington's disease patients, lower IGF-1 levels were associated with reduced gray matter in fronto-temporal and subcortical regions (p<0.05 corrected).

Conclusion: Based on these preliminary findings, hypothalamic function, specifically IGF-1, might have an impact on social cognition and brain structure in Huntington's disease.

Disclosure: We are grateful to all participants for their time and efforts.
Objective: We aim to use a small PD patient dataset with wearable movement tracker data to learn broadly-applicable L-dopa medication strategies. We then aim to demonstrate that these strategies can improve outcomes for PD patients who do not have access to wearable movement trackers.

Background: Effective treatment of Parkinson’s disease (PD) is a continual challenge for healthcare providers, and emerging technologies can assist physicians in providing state-of-the-art PD care. Wearable movement trackers have shown recent promise in measuring the severity of PD patients' symptoms, but not all patients may have access to these trackers. Given the recent success of machine learning in treatment optimization, it is worth investigating whether machine learning can derive medication strategies from wearable datasets that generalize to patients without access to wearables.

Method: We leverage a small dataset of n=26 PD patients who wore wrist-mounted movement trackers for two separate six-day periods. We use these patients' symptom readings to model how these patients' bradykinesia and dyskinesia levels respond to L-dopa administration. We then use reinforcement learning (RL) to learn optimal L-dopa dosing strategies for these patients. Lastly, we test our RL-based L-dopa strategies using n=399 PD patients from the Parkinson's Progression Markers Initiative (PPMI) dataset, for whom wearable data was not available.

Results: Our wearable-based RL policies suggest that the original n=26 study patients would experience lower bradykinesia (and unchanged dyskinesia) if switched to controlled-release L-dopa formulations such as Rytary. Applying this wearable RL-based strategy to the PPMI patients (who have a baseline UPDRS-Part III score of 20.8) is predicted to yield an average UPDRS-Part III increase of only 0.75 points over the study period. This compares with an estimated 1.94 point increase under patients' originally-prescribed medication regimens, suggesting a 1.19 point improvement under our wearable framework (paired t-test p-value<0.001). Furthermore, 20.1% of PPMI patients are predicted to experience clinically meaningful improvement of at least 2 points, compared with their originally-prescribed regimens. By comparison, training RL policies directly from the PPMI dataset (i.e., without wearable data) yields only a 0.54 point improvement compared with originally-prescribed regimens (which does not significantly differ from zero), with only 13.6% of patients experiencing clinically meaningful improvement.

Conclusion: We show that pairing machine learning with even small quantities of wearable movement tracker data can offer novel, generalizable clinical insights and medication strategies, which can be used to improve care for other PD patients for whom wearable data are not available.

Disclosure: Data used in this article were obtained from the Parkinson Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). For up-to-date information on the study, visit www.ppmi-info.org. PPMI is sponsored by the Michael J. Fox Foundation for Parkinson’s Research (MJFF) and is co-funded by MJFF, Abbvie, Allergan, Avid Radiopharmaceuticals, Biogen, BioLegend, Bristol-Myers Squibb, Celgene, Denali, Eli Lilly Co., F. Hoffman-La Roche, Ltd., GE Healthcare, Genentech, GlaxoSmithKline, Lundbeck, Merck, MesoScale, Piramal, Prevail Therapeutics, Pfizer, Roche, Sanofi Genzyme, Servier, Takeda, Teva, UCB, Berily, and Voyager Therapeutics.
LBA-7: alpha-synuclein seed amplification assay performance in 1,139 cases: results from the PPMI Study


Objective: To evaluate alpha-synuclein seed amplification assay (SAA) performance in CSF samples from a large cohort of patients with PD, individuals at-risk for PD and healthy controls.

Background: Biomarkers that confirm early diagnosis or indicate risk for Parkinson’s disease (PD) are needed for clinical care and to accelerate therapeutic development.

Method: The Parkinson Progression Marker Initiative (PPMI) study is a multi-national observational study of deeply phenotyped PD patients, at risk individuals including patients with hyposmia and/or REM sleep behavior disorder (RBD), non-manifesting carriers (NMC) of PD genes (eg. LRRK2, GBA) and healthy controls. Participants have regular clinical evaluations, dopamine imaging and biofluid collection. SAA analysis was performed using reported methods (Amprion, Inc.) on previously collected samples. We assessed sensitivity and specificity in PD patients and healthy controls, including PD subgroups (men vs. women, genetic variant carriers, subjects with and without olfactory deficits), and determined the frequency of positive CSF SAA results in prodromal subjects (RBD and hyposmia) and NMCs.

Results: 1,139 participants were included in this analysis including 557 patients with PD, 163 HCs, 55 SWEDDs, 51 prodromal subjects and 313 NMCs. Sensitivity and specificity in PD patients and HCs were 88% and 96% respectively. Sensitivity in PD with typical olfactory deficit was 98%. Sensitivity was lower in certain subgroups including LRRK2 carriers (67%) and PD patients without olfactory deficit (71%). The subgroup with the lowest sensitivity was female LRRK2 carriers without olfactory deficit (23%). Among prodromal and at-risk groups, 86% of RBD and hyposmic cases has positive SAA. 8% of NMC (LRRK2 and GBA) were positive. DAT imaging was within normal limits in 29/65 at risk individuals with positive SAA results.

Conclusion: Our results confirm the diagnostic accuracy for PD of a-syn SAA from CSF in typical PD and demonstrate that SAA is positive in a majority of prodromal cases and a smaller fraction of at-risk NMCs. These findings along with the variability among subgroups indicate that SAA may be a crucial, early biomarker to establish homogeneous at risk cohorts for observational and interventional studies.

Disclosure: Data used in the preparation of this article were obtained from the Parkinson’s Progression Markers Initiative (PPMI) database (www.ppmi-info.org/access-data-specimens/download-data). For up-to-date information on the study, visit ppmi-info.org.

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LBA-8: Detection of seeding capacities of blood-derived α-synuclein from prodromal Parkinson’s disease converters


Objective: Identifying seeding capacities of soluble α-synuclein (α-syn) conformers derived from neuronal extracellular vesicles (NEs) from prodromal Parkinson’s disease (PD) converters.

Background: The synaptic protein α-syn is able to form toxic oligomers as well as insoluble amyloid fibrils and causes cell death of neurons. This pathology can be transmitted from cell to cell. By the time cardinal motor-symptoms allow the clinical diagnosis of PD an extensive loss of dopaminergic neurons has already taken place in a process spanning many years. In this prodromal phase several clinical markers with predictive value for PD have been described, but they are limited due to their varying, mostly low specificity. Individuals at-risk for PD serve as an important target group for detecting of disease specific biomarkers.

Method: We studied participants from the ‘Tübingen evaluation of risk factors for early detection of Neurodegeneration’-study (TREND), a prospective longitudinal study, to assess natural history and pathology of PD as well as to provide predictive models of progression. We analyzed seeding capacities of soluble NE-derived α-syn from 12 at risk individuals that developed PD over the course of the study and 12 controls at baseline and up to four time points longitudinally. Here we used an adjusted α-syn seeding assay and validated end products by immunoblots. Next, we correlated the seeding capacities observed to several clinical markers.

Results: For all PD patients we observed an increasing seeding capacity years before clinical diagnosis resulting in in a similar seeding range at the time of clinical diagnosis. In the control cohort no seeding capacity was measured. A positive correlation between motor scores and the seeding values could be detected.

Conclusion: We here demonstrate for the first time that α-syn seeding in blood derived NEs can be detected years before diagnosis which thus has the potential for a reliable blood biomarker for PD pathology years before clinical diagnosis.

LBA-9: Initiating dopamine agonists rather than levodopa in early Parkinson’s disease does not delay the need for DBS.

D. Olszewska, A. Fasano, R. Munhoz, C. Ramirez-Gomez, A. Lang (Canada)

Objective: To determine whether there is a difference in time between initial levodopa vs dopamine agonists (DA) treatment and the development of disabling motor complications (MC) prompting consideration of deep brain stimulation (DBS).

Background: While levodopa is the most effective symptomatic treatment for Parkinson’s disease (PD), its use is associated with an increased risk of MC in the first five years of treatment compared to DA first
therapy. It is not known whether the early delay in MC with initial DA therapy translates into important delays and true benefit with respect to disabling MC that are the major indication for DBS later on.

Method: We performed a large retrospective cohort study of 1627 PD patients attending DBS clinic at Toronto Western Hospital, Canada between 03/2004-02/2022. PD patients who underwent globus pallidus interna (GPI) or subthalamic nucleus (STN) DBS in 2005 or later to address disabling MC were included. 1189 did not meet the inclusion criteria.

Results: Of 438 patients included, 352 patients underwent STN DBS, 86 GPI. The median disease duration was 9 years (range 2-30). 312 patients received levodopa first and 126 a DA. There was no statistically significant difference in the target selection, or amantadine use between the groups. The duration from the first treatment to assessment for DBS (L-dopa median 8, IQR 4; DA median 9, IQR 4) or DBS surgery (L-dopa median 10, IQR 5; DA median 10, IQR 5), did not significantly differ, and the results were not influenced by the age-at-diagnosis, gender, or amantadine use (first treatment to DBS assessment, p=0.64; first treatment to surgery, p=0.759) (Fig. 1).

In two longest studies to date, only 1/5 of the original cohort after 14 years of follow-up and 1/3 after 15 years was available for an assessment.1,2 Importantly, these studies were conducted before DBS was an established treatment for disabling MC in PD. Large studies including younger patients at greater risk of MC and with more intermediate duration of disease, when MC can result in clear disability, are lacking. Our study included 49% of individuals diagnosed at age ≤ 50, with a long follow up, sufficient to allow the development of disabling MC, but without major mortality/morbidity preventing surgery. Our final sample size (n=438) was over two times larger than three of the longest studies combined at the time of the last follow up. 1-3

Conclusion: This is the only study to date to evaluate the duration between L-dopa or DA first treatment and the development of MC of sufficient severity to warrant consideration of DBS. The results suggest that the development of disabling motor complications warranting DBS is independent of the type of first dopaminergic treatment.

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LBA-10: Effects of disease duration on response inhibition in Parkinson’s disease are mediated by enhanced beta power in the motor cortex

H. Strenger, N. Salehi, A. Moersdorf, V. Hardt, A. Petersen, E. Kusche, L. Timmermann, I. Weber, C. Oehrn (Germany)

Objective: To investigate neural oscillations underlying response inhibition in Parkinson's disease (PD) and the effects of medication and patient characteristics.

Background: Neuropsychiatric side effects are common in PD and often caused or aggravated by dopaminergic medication. Several studies suggest alterations of response inhibition, a proxy of impulsivity, in PD that can be affected by dopaminergic medication. However, the direction of reported effects varies. While disease duration was identified as a confounding factor, the role of sequence effects of off/on medication states and the salience of stimuli is still unclear. Here, we address these shortcomings investigating the neural signature of response inhibition using a multivariate analysis approach.

Method: We obtained high-density electroencephalography in 24 patients with PD and 24 age- and sex-matched healthy controls (HC). Patients performed a go/no-go task on two separate days on and off their usual medication in a pseudo-randomized order. The paradigm included infrequent go-trials to control for effects of stimulus salience. We assessed behavioral outcomes by means of a linear regression and compared power of neural oscillations (2-150 Hz) using non-parametric cluster based permutation analysis with the factors group (PD vs. HC) and trial type (infrequent go vs. no-go).

Results: Multiple linear regression showed that medication improved response inhibition as a function of disease duration (p=.046). Solely in the on medication state, cluster analyses revealed a time- and frequency-specific interaction effect between trial type and group on beta oscillations in the right motor cortex around response time (0.4-0.6ms, 13-30Hz, p=.02). During go trials, beta power of PD patients was not different from HC. During no-go trials, however, PD patients showed a relative increase in beta power over motor-related areas compared to HC. Spearman correlation shows that cortical beta power enhancement in PD patients during response inhibition increased as a function of disease duration on (R=.51, p=.01), but not off medication (R=.22, p=.31, in line with the behavioral results.

Conclusion: Results indicate that dopaminergic medication improves response inhibition in PD patients with longer disease duration, which is associated with enhanced beta power in the motor cortex.

LBA-11: NIHR Global Health Research Group on Transforming Parkinson’s Care in Africa

C. Dotchin, N. Fothergill-Misbah, N. Okubadejo, R. Walker (United Kingdom)

Objective: To outline an exciting and ambitious new collaboration and the creation of a Global Health Research Group on Parkinson's disease.
To inform the MDS International Congress audience of the opportunities that this grant will afford, through potential for collaboration and capacity building.

Background: The population of sub-Saharan Africa is ageing faster than anywhere in the world, with a large increase in age-related diseases. There are very few medical specialists, and access to effective and affordable drug treatment is very limited. There is a lack of awareness about PD; people often don’t recognise symptoms, or access medical help, and may not be correctly diagnosed. Some see traditional, or faith, healers and many seek no help at all, mistaking the symptoms for ageing.

Method: The group includes sites in Tanzania, Kenya, Ghana, Nigeria, South Africa, Ethiopia and Egypt to:

Improve diagnosis –
1. Develop diagnostic aids, utilise innovative techniques, investigate chemicals in blood, sweat and urine as early markers of PD, and conduct microbiome analyses
2. Provide training for doctors, nurses and therapists
3. Develop and trial services for diagnosis and management of PD by non-specialists
4. Undertake community-based door to door prevalence studies in Tanzania, Ghana, Nigeria and Kenya, testing screening tools

Improve care -
5. Create a database of PD patients across the sites with detailed phenotype, treatment response and outcome data
6. Investigate effectiveness and side-effects of Mucuna pruriens (MP), a tropical plant containing levodopa, compared to standard Levodopa in Tanzania
7. Assess response to drug treatment, with non-invasive and low-cost home monitoring via wearable movement sensors
8. Work with patient and carer support groups to investigate the lived experiences and raise public awareness
9. Contribute samples to the Global Parkinson’s Genetics Programme for genetic analyses

Results: The 4-year study will begin in August 2022, with recruitment commencing early 2023. The inaugural face to face meeting of investigators will be held in Madrid, alongside this conference.

Conclusion: This study will be the first of its kind in Africa, uniting researchers across the continent with global field leading researchers. It will shed light on the epidemiology and genetics of PD and deliver the possibility of timely, accurate diagnosis, access to treatment, monitoring and follow up, alongside increasing capacity to train clinical and research staff to achieve the goal that no one with PD is left behind.
LBA-12: Ontology-based, Real-time, Machine learning Informatics System for Parkinson Disease (ORMIS-PD)

D. Gupta, K. Prantzalos, A. Hiller, B. Lobb, K. Chan, J. Boyd, S. Sahoo (USA)

Objective: To describe the design and development of ORMIS-PD and demonstrate its underlying components of Parkinson and Movement Disorders Ontology (PMDO) and data entry module.

Background: The Movement Disorders Society clinical diagnostic criteria for PD (MDS-PD criteria) allow classification of a Parkinson disease (PD) patient into “clinically established” and “clinically probable” level of diagnostic certainty with high sensitivity and specificity. However, there is currently no clinical decision support (CDS) tool available to implement these criteria at the point-of-care.

Method: As part of a collaborative research project funded by the US Department of Defense, we are developing ORMIS-PD as a PMDO-based clinical research informatics system for automated PD diagnostication and prognostication. The ORMIS-PD consists of three modules (data entry, knowledge base, data analytics) and its key knowledge source is the PMDO.

The PMDO was designed using an iterative collaborative process with movement disorders specialists as well as ontology engineering best practices that included use of structural metrics to evaluate the information content of the ontology and identify modeling errors and improve the structure of class hierarchy.

The current functional prototype of ORMIS-PD’s data entry module has been developed using an agile methodology and Django web development framework (figure 1), and it supports minimum data capture needed to classify a PD patient on the MDS-PD criteria.

Results: The PMDO uses the Basic Formal Ontology (BFO) as a reference upper-level ontology, and its current version has at least 468 classes and their associated properties to represent various terms and concepts used in the MDS-PD criteria, PD-relevant NIH Common Data Elements (CDE), and clinical evaluation for new diagnosis of PD. The PMDO is available in the repository of National Center for Biomedical Ontologies at this web link: https://bioportal.bioontology.org/ontologies/PMDO

The tab-based graphical user interface of the data entry module has eleven sections (demographics, motor symptoms, non-motor symptoms, family history, social & environmental history, occupational & military history, health profile, medications, exam, scales, domain-specific information, and diagnostics), and it supports input data validation, logical skip patterns, dynamic table interfaces, and database support.

Conclusion: We report and demonstrate the foundational elements of ORMIS-PD as a precursor to a CDS tool for implementation of the MDS-PD criteria for an individual patient in the clinic and clinical trials.
LBA-13: Expression of Prokineticin-2 is increased in olfactory neurons of Parkinson’s disease patients and directly correlates with accumulation of α-synuclein oligomers


Objective: To shape the activity of Prokineticin-2 (PK2) pathway and define correlations with synucleinopathy in olfactory neurons (ONs) of patients with Parkinson’s disease (PD) at different disease stages.

Background: PD is still an incurable disorder, urgently needing novel neuroprotection targets. PK2 is a chemokine-like peptide, which displayed, in experimental models of PD, interesting neuroprotective properties for early stages of neurodegeneration. However, dynamics of PK2 pathway in PD patients remain unknown. PK2 is preferentially expressed into the olfactory system, which is also one of the earliest sites of neuropathology in PD. ONs can be easily collected, being suitable for molecular analysis.

Method: ONs were withdrawn by non-invasive mucosa brushing from n=38 PD patients (n=26 de novo, newly-diagnosed and untreated) and n=21 sex/age matched healthy controls. Patients were evaluated by H&Y scale, MDS-UPDRS pars III, non-motor symptoms and cognition scores, LEDD calculation. ONs were assessed by Real Time-PCR to measure expression levels of PK2 and other PK2 pathway-related factors (PK2 receptors type 1 and 2, PK2-long peptide); immunofluorescence was performed to quantify PK2 and α-synuclein species (total and oligomeric).

Results: ONs PK2 expression was significantly augmented in PD compared to controls; levels were higher in de novo patients than those more advanced. In de novo group, PK2 expression was directly associated
with MDS-UPDRS pars III. The oligomeric α-synuclein specie, but not the total one, was higher in PD patients than controls. Oligomeric α-synuclein and PK2 directly correlated in PD group.

Conclusion: PK2 pathway was activated in ONs of patients with PD, mostly at early phases and proportionally to motor disturbances. PK2 expression reflected oligomeric α-synuclein accumulation, probably as a defensive reaction, which supports the value of PK2 as a neuroprotection target for PD. ONs resulted a valuable tissue to examine molecular events underlying PD and a reliable source for biomarkers.

**LBA-14: Migraine increases the risk of Parkinson’s disease in the middle-aged and older population: A nationwide cohort study**

M. Baek, W. Ha, J. Hong, K. Han (South Korea)

**Objective:** To investigate the incidence and risks of Parkinson’s disease (PD) in the patients with migraine among the middle-aged and older population.

**Background:** Previous studies on the association between Parkinson’s disease and migraine showed inconsistent findings. In this study, the effects of migraine on incident Parkinson’s disease were investigated using a large dataset encompassing the medical records of the nation-wide population of the Republic of Korea.

**Method:** We analyzed the incidence of PD in the individuals with or without migraine retrospectively, using the Korean National Health Insurance Service database. A total of 6,093,904 individuals aged 40 or older were enrolled among those who were registered in the national health screening program in 2009. The patients with migraine were defined using the International Classification of Diseases, 10th revision (ICD-10) code G43 in 2009, and the individual without migraine were defined as who have no records of migraine diagnosis from 2002 to 2008. Individuals who were newly diagnosed with PD were selected using the ICD-10 code G20 and registration code V124 in the program for rare intractable diseases.

**Results:** A total of 214,193 individuals with migraine and 5,879,711 individuals without migraine were included in the study. During 9.1 years of follow-up (55,435,626 person-years), 1,973 individuals among 214,193 individuals (0.92%) with migraine were newly diagnosed with PD, while 30,664 individuals among 5,879,711 (0.52%) individuals without migraine were newly diagnosed with PD. The risk of PD was 1.35-folds higher in the individuals with migraine than those without migraine after adjustment for covariates. The incidence of PD was higher in the individuals with the chronic migraine than in those with the episodic migraine group (HR, 2.36 [95% CI, 2.20-2.54]). In male, underlying dyslipidemia increases the risk of PD in the individuals with migraine (P for interaction = 0.012), while in female, younger age increases the risk of PD in the individuals with migraine (P for interaction = 0.038).

**Conclusion:** This study found the association between migraine and the incidence of PD in the middle-aged and older population.
LBA15: The UP Study confirms the neuroprotective potential of ursodeoxycholic acid (UDCA) in Parkinson’s disease

Objective: 1. To determine the safety and tolerability of 30mg/kg of ursodeoxycholic acid (UDCA) in early Parkinson’s disease (PD, primary outcome).

2. To evaluate the disease modifying potential of UDCA by combining subjective clinical rating scales with objective, in-depth motion sensor-based quantification of motor impairment.

3. To assess target engagement of UDCA using midbrain 31phosphorus magnetic resonance spectroscopy (31P-MRS).

4. To assess changes in serum bile acid composition in response to UDCA treatment.

Background: Mitochondrial dysfunction is a key pathogenic mechanism for PD. We previously identified UDCA as a powerful mitochondrial rescue compound in the first screen of an entire compound library in PD patient tissue. UDCA has been in clinical use for liver disorders for decades and is therefore an ideal candidate for the drug-repurposing strategy.

Method: The UP (UDCA in PD) study was a phase Ila, randomised, double-blind, two centre, placebo-controlled trial of high dose ursodeoxycholic acid (30mg/kg) in 30 participants with early PD for 48 weeks followed by an 8-week washout period. Randomisation was 2:1 drug to placebo.

Results: UDCA was safe and extremely well tolerated with excellent compliance. There were no serious adverse events in the treatment group. Only mild, transient gastrointestinal adverse events were observed more frequently in those taking UDCA compared to placebo. Bile acid analysis confirmed a marked, stable increase of UDCA and its key conjugates throughout the treatment period. Objective quantification of motor impairment demonstrated improvement of several gait parameters such as cadence (p=0.019), stride time (p=0.031), stride time variability (p=0.031), stance time (p=0.031) and stance time variability (p=0.024) in the UDCA treatment group compared to placebo. In contrast, subjective clinical assessment using standard clinical rating scales failed to detect any difference between treatment groups. Midbrain 31P-MRS revealed an improvement in Gibb’s free energy of ATP hydrolysis in the UDCA group compared to placebo (p=0.024).

Conclusion: The UP Study demonstrates the utility of both sensor-based quantification of motor impairment and 31P-MRS in early phase clinical trials and provides justification for subsequent larger trials to further evaluate the disease-modifying effect of UDCA in PD.

LBA-16: Anatomical correlates for DBS effects on heading perception in Parkinson's disease

S. Beylergil, C. McIntyre, C. Kilbane, A. Shaikh (USA)

Objective: Finding anatomical correlates that modulates self-motion perception in Parkinson's disease (PD).

Background: Perception of our linear motion, heading, is critical for postural control, gait, and locomotion. The heading perception, in the paucity of accurate visual input, is significantly impaired in
PD. Deep brain stimulation (DBS) has variable effects on vestibular heading perception, the effects depend on the location of the electrodes within the subthalamic nucleus (STN).

Method: In 14 PD patients with bilateral STN DBS, and matched controls, we used state-of-art six-degrees-of-freedom motion platform, immersive virtual reality, and patient-specific computer DBS models, asking the following questions.

1) Which areas of STN stimulation modulate vestibular heading perception in PD?
2) Which pathways within or in the vicinity of the STN modulated vestibular heading perception?

Results: Objective assessment of heading perception with psychometric function curve revealed that PD participants have significantly lower accuracy and increased threshold for perceiving the direction of their motion. Bilateral STN DBS significantly improves directional discrimination accuracy and threshold in the rightward direction but there is no change for leftward motion. We found that patients with large overlaps between the DBS-induced volume of tissue activation (VTA) and the STN in their left hemisphere had a positive impact on rightward heading perception; there was an improvement in threshold and accuracy. We also found a positive association with improved discrimination threshold in the right-sided heading and the percentages of activated streamlines of the contralateral GPe-STN, GPI-STN, M1-HDP, premotor-HDP, and SMA-HDP pathways. Additionally, DBS-induced improvement in the right discrimination threshold was correlated with the distance between the centers of VTA and the STN positively along the x-axis and negatively along the y-axis. That is to say, the discrimination threshold for the right-sided heading seemed to improve as the center of VTA was located more medially and posteriorly to the STN in the left hemisphere.

Conclusion: Our study objectively identified regions of STN and pathways around the STN that can effectively modulate the perception of one’s linear motion, and heading. The results have direct clinical implications for effective DBS placement and stimulation for the treatment of postural, balance, and locomotive abnormalities in PD.

LBA-17: Early combination of amantadine to L-DOPA in Parkinson disease: the PREMANDYSK study

O. Rascol (France)

Objective: Primary objective: to assess if the early combination of amantadine (200 mg/d) within 1 year of L-DOPA in early PD reduces the prevalence of dyskinesia over 18 months.

Secondary objectives: to assess if such potential reduction in L-DOPA-induced dyskinesia rate is related to a short- or long-lasting effect.

Exploratory objectives: to assess if induces significant changes in L-DOPA daily doses and severity of motor and non-motor symptoms.

Background: Amantadine in an original antiparkinsonian medication with a dual (dopaminergic and glutamatergic) mechanisms of action.
It is approved for the treatment of PD at any stage of the disease, based on out-dated low-quality RCTs, except for its efficacy in reducing the severity of established L-DOPA-induced dyskinesia in the advanced stage of PD.

Its impact on the development of dyskinesia when used early in PD is unknown. Moreover, its efficacy on motor and non-motor symptoms in the early stages of PD, when combined to L-DOPA, remains poorly known.

Method: This was a 23-month multicentric, prospective, randomized, placebo-controlled, double-blind parallel-group study conducted in 207 (amantadine 200 mg/d: n=99; placebo: n= 108) patients with early PD, treated with L-DOPA for less than 1 year and free of dyskinesia and motor fluctuations at baseline.

The main outcome measure was the proportion of patients having developed dyskinesia. Patients were followed during 3 consecutive Phases:

- Phase 1 (from baseline to month-18) to compare the prevalence of dyskinesia after 18 months of exposure in both arms (primary outcome).
- Phase 2 "delayed-start" (from month-18 to month-21) when all patients were receiving amantadine to compare dyskinesia prevalence at the end of Phase 2 (secondary outcome)
- Phase 3 "wash-out" (from month-21 to month 23) when all patients were receiving placebo, to compare dyskinesia prevalence at the end of Phase 3 (secondary outcome).

Phase 2 and 3 were designed to assess if the the effect of amantadine on dyskinesia could be related to a short-lasting or a long-lasting effect

Exploratory outcomes included changes from baseline to month-18 (Phase 1) in L-DOPA daily dose, and motor and non-motor symptoms using corresponding validated scales (MDS-UPDRS, NMSS (Chaudhuri et al, 2007), freezing of gait (FOG, Giladi et al 2000), behavior disorders (Ardouin et al, 2009), fatigue (Brown et al, 2005), apathy (Sockeel ret al, 2006), Quality of life (PDQ-8, Katsarou et al, 2004) and Cognitive dysfunction (MOCA)

Results: The primary outcome was met with significantly less dyskinesia at month-18 on amantadine (11%) than placebo (22%) (95%CI -21%; -1%, p=0.02)

There was no significant difference in secondary out-comes at Phase 2 and 3

During Phase 1, L-DOPA daily dosage increased significantly less on amantadine (+36±171 mg/d) than placebo (+92±189 mg/d; treatment effect: -56mg/d [95% CI -105 mg/d;-6 mg/d], p=0.03). There were no significant change from baseline to month-18 in MDS-UPDRS III scores (amantadine: +1.4±7.4; placebo: +2.1±8.0, p=0.45) while significant improvements in favor of amantadine over placebo were observed for freezing of gait (-1.8 [-3.0 to -0.7]; p=0.002), fatigue (-4.5 [-8.6 to -0.5]; p= 0. 03) and quality of life (-1.5 [-2.6 to -0.3]; p=0.01)

Conclusion: The PREMANDYSK trial showed that amantadine (200 mg/d adjunct to L-DOPA within the first year of L-DOPA-therapy) significantly reduced by 50% the risk of developing L-DOPA-induced
dyskinesia after 18 month of treatment. The mechanism of this effect may involve NMDA antagonism and/or sparing of L-DOPA dose, while long-term benefit could not be demonstrated.

Amantadine significantly reduced the need to increase L-DOPA by ≈ 50 mg/day after 18 month of exposure, which may have masked a modest dopaminergic motor symptomatic effect as assessed by MDS-UPDRS score. In contrast, and in spite of this lower dose of L-DOPA concommittent treatment, mild but significant improvements were observed on freezing of gait, fatigue and QoL scores, which may be related to non-dopaminergic amantadine properties.

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**LBA-18: Immunoproteasome mRNA as a novel biomarker for Parkinson’s disease**

H. Nguyen, Y. Kim, I. Kwak, Y. Kim, T. Nguyen, Y. Lee, H. Ma (South Korea)

Objective: To determine if immunoproteasome mRNA in peripheral blood mononuclear cells (PBMCs) is different between PD and healthy control (HC) and to test its value as a biomarker of PD.

Background: The ubiquitin-proteasome system (UPS) is the major non-lysosomal protein degradation system and is critical for cellular proteostasis including the degradation of the misfolded α-synuclein protein. Immunoproteasome, a type of proteasome derived from the constitutive proteasome, is abundantly expressed in immune cells. Although tons of evidence suggests that immune dysfunction has a role in Parkinson’s disease (PD) in recent years, the relationship between immunoproteasome and PD was not evaluated clearly. Therefore, we hypothesized that the shift of immunoproteasome appears in the patients with PD, because it plays roles in both the immune system and protein homeostasis.

Method: Blood samples were collected from 14 HC and 41 patients with PD of comparable ages. In PD group, there were 21 patients with the Hoehn and Yahr stage (H & Y) ≤ 2.5 and 20 patients with H&Y ≥ 3. PBMCs were isolated immediately after blood collection and followed by RNA extraction (Trizol method). RT-qPCR was performed to measure the mRNA levels of three catalytic subunits of immunoproteasome including PSMB8, PSMB9, and PSMB10.

Results: Whilst the level of PSMB8 mRNA in the PD group was elevated and the PSMB10 mRNA level was decreased compared with the HC group significantly (p < 0.05 and < 0.01 respectively), the level of PSMB9 mRNA was not different between PD and HC. (Figure 1. A-C) We used the ratio of PSMB10 and PSMB8 (PSMB10/8) in representing the changes of immunoproteasome mRNA levels in PD patients. The ratio of PSMB10/8 showed a significant decrease in patients with PD compared to HC (p < 0.001). (Figure 1. D) Besides, we found a correlation between the PSMB10/8 ratio and UPDRS Part III score in early stage of PD with H&Y stage ≤ 2.5 (r = 0.375, p < 0.05). Eventually, analysis using the receiver operating characteristic (ROC) curve indicates that the PSMB10/8 ratio can discriminate PD from HC with 85.7% sensitivity and 87.8% specificity (cut-off value = 0.844) and an area under the curve (AUC) of 0.862. For distinguishing early stage of PD (H&Y ≤ 2.5) from HC, this novel marker can gain 85.71% sensitivity and 90.48% specificity (cut-off value = 0.844) with AUC of 0.881.
Conclusion: Immunoproteasome PSMB8 and PSMB10 mRNA level was changed in PD, and the ratio of PSMB10/8 mRNA levels would be a valuable biomarker for differentiating PD from HC.

LBA-19: Genome-wide determinants of mortality and clinical progression in Parkinson’s disease


Objective: The genetic basis of clinical progression Parkinson’s disease (PD) remains largely unknown. We performed genome-wide association studies (GWASs) to identify variants associated with progression to mortality, Hoehn and Yahr stage 3 or greater, and cognitive impairment in Parkinson’s disease.

Background: Understanding the biology of PD progression is important for defining mechanisms that can be used to develop new treatments. Only in recent years has clinical progression data become available in large longitudinal cohorts. Large-scale GWASs have identified 90 risk variants for PD, but only 5 loci have been nominated for PD progression.

Method: We analysed data from 11 cohorts with 6,766 PD patients, over 15,340 visits with a mean follow-up of between 4.2 and 15.7 years. We carried out a genome wide survival study for time to motor progression, defined by reaching Hoehn and Yahr stage 3 or greater, cognitive impairment as defined by serial cognitive examination, and death (mortality).

Results: There was a robust effect of the APOE ε4 allele on mortality and cognitive impairment in PD. We identified three novel loci for mortality and motor progression, and nominated genes based on physical proximity or expression quantitative trait loci data. One locus within the TBXAS1 gene, encoding thromboxane A synthase 1, was significantly associated with mortality in PD (Hazard Ratio = 2.0, p-value = 7.7 x 10E-10). Another locus, near the SYT10 gene encoding synaptotagmin 10, was associated just below genome-wide significance (HR = 1.4, p-value = 5.3 x 10E-8). We also identified a locus with lead SNP rs112809886 which was associated with progression to Hoehn and Yahr stage 3 or greater (HR = 4.8, p = 1.9 x 10E-9). This locus is near GGT5 but regulates expression of ADORA2A in the cerebellum. ADORA2A encodes the adenosine A2A receptor, which is highly expressed in GABA-ergic striatal-pallidal neurons. This receptor is the target of the A2A receptor antagonist istradefylline, which has been licensed as a treatment of PD in Japan and the US.

Conclusion: We report three novel loci associated with PD progression or mortality. Further work is needed to replicate these loci in other independent cohorts, as well as to understand which are the causal variants and how they affect underlying disease biology. However these genes and pathways may represent new candidates for disease modification in PD.
LBA-20: Association between the LRP1B and Parkinson’s disease dementia


Objective: To explore the genetic factors associated with rate of progression to Parkinson’s disease dementia.

Background: Parkinson’s disease is one of the most common age-related neurodegenerative disorders. Although predominantly a motor disorder, cognitive impairment and dementia are important features of Parkinson’s disease, particularly in the later stages of the disease. However, the rate of cognitive decline varies widely among Parkinson’s disease patients, and the genetic basis for this heterogeneity is incompletely understood.

Method: We performed a genome-wide survival meta-analysis of 3,964 clinically diagnosed Parkinson’s disease cases of European ancestry from four longitudinal cohorts.

Results: In total, 6.7% of individuals with Parkinson’s disease developed dementia during study follow-up, on average 6.67 +/- 3.37 years from disease onset or diagnosis.

We have identified the APOE-ε4 allele as a major risk factor for the conversion to Parkinson’s disease dementia [hazards ratio = 2.42 (1.95–3.01), P = 1.21x10^-15], as well as three new loci, including the ApoE and APP receptor LRP1B [hazards ratio = 3.37 (2.23–5.09), P = 7.39x10^-09]. Additionally, variants in SLC6A3 [hazards ratio = 4.42 (2.62–7.45), P = 2.32x10-08] and near SSR1 [hazards ratio = 2.31 (1.72–
3.11), $P = 2.44 \times 10^{-08}$ were associated with faster progression to dementia with genome-wide significance. CSF biomarker analysis also implicated the amyloid pathway in Parkinson’s disease dementia, with significantly reduced levels of amyloid β42 ($P = 0.001193$) in the latter group compared to Parkinson’s disease without dementia.

Conclusion: These results identify new candidate genes associated with faster conversion to dementia in Parkinson’s disease and suggest that amyloid-targeting therapy may have a role in preventing Parkinson’s disease dementia.

LBA-21: 7T resting-state functional MRI default mode network connectivity in Parkinson’s disease patients with mild cognitive impairment

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Objective: This study aims to investigate whether Mild Cognitive Impairment in Parkinson's Disease is associated with an altered functional connectivity in the Default Mode Network.

Background: Parkinson’s disease is well-known for its motor symptoms. However, in the past decade there is growing interest in non-motor symptoms including mild cognitive impairment, were the default mode network is believed to play a central role in. The novel 7T resting-state functional MRI is a valuable method to assess the potential of the default mode network as a biomarker for mild cognitive impairment in Parkinson's Disease.

Method: Forty-two healthy controls, 78 cognitive unimpaired Parkinson's Disease patients and 20 mild cognitive impairment PD patients were evaluated and a 7T resting-state functional MRI scan was acquired. Imaging pre-processing was done using a FMRIB software library (FSL) pipeline. Respiration and cardiac pulse were measured during scanning and taken as confounders. Default mode network functional connectivity differences between groups were analysed using non-parametric permutation testing (1000 tests) with age, brain volume and levodopa equivalent daily dose (LEDD) as confounders.

Results: Functional image pre-processing produced an acceptable dataset suitable for analysis. MCI Parkinson's Disease patients showed a significant smaller brain volume and a significant higher UPDRS-III score compared to Cognitive Unimpaired Parkinson's Disease patients. No significant differences in Default Mode Network functional connectivity were found between Parkinson's Disease-mild cognitive impairment and Parkinson's Disease-Cognitive Unimpaired patients. Furthermore, no significant differences in Default Mode Network functional connectivity were observed between Healthy Controls and both Parkinson’s Disease groups.

Conclusion: This study showed that there were no significant differences in default mode network functional connectivity between mild cognitive impaired and cognitive unimpaired Parkinson’s disease patients measured with a 7T rsfMRI while correcting for physiological parameters. These results contrast previous studies with lower MRI field strengths in smaller datasets. Therefore, future work is needed to clarify the role of the Default Mode Network as possible biomarker for mild cognitive impairment in Parkinson's Disease and to investigate the predicting value over time in longitudinal data.
LBA-22: Subthalamic stimulation in the theta and gamma frequency band improves working memory in patients with Parkinson’s disease

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Objective: To assess frequency-specific effects of deep brain stimulation (DBS) on working memory (WM) performance in Parkinson’s disease (PD).

Background: DBS in the subthalamic nucleus (STN) can affect cognitive functions. There is no conclusive evidence regarding the effect of DBS on WM. This key cognitive function is associated with oscillations in the theta and gamma frequency range and first small studies indicate that theta DBS can improve executive functions. Here, we hypothesize that specifically theta and gamma frequency STN DBS improve WM.

Method: In this single-blind, randomized study, we assessed the behavioral outcome of DBS in the theta (6 Hz), alpha/beta (15 Hz), low gamma (70 Hz) and high gamma (clinical stimulation frequency, 130 Hz) frequency range on performance in a WM numeric task in comparison to no stimulation. 20 PD patients (4 females, mean±SD age 57.1±6.6) with chronic bilateral STN-DBS performed the task after 12 hours withdrawal of dopaminergic medication. We applied stimulation conditions in a randomized order without altering the individual clinical stimulation amplitude. An independent clinician rated parts of UPDRS III during each condition. We assessed behavioral effects using a generalized linear mixed effects model.

Results: We did not find a main effect of stimulation frequency on WM performance, but an interaction between frequency and levodopa equivalent daily dose (LEDD, t2305=-3.71, p<.001). Post-hoc Pearson correlations between stimulation frequency effects (WM performance stim on-off) and LEDD revealed that stimulation effects at the theta and lowgamma frequency depended on LEDD (R2=-0.57, p=.01; R2=-0.55, p=.01; R2= -0.45, p=.04), but STN DBS at the alpha/beta frequency did not (R2= 0.17, p=0.46). A median split of the data based on LEDD revealed specific effects of theta and gamma frequency stimulation on WM in patients with low LEDD. WM performance did not correlate with UPDRS III subscores.

Conclusion: Our results demonstrate a frequency-specific effect of STN DBS in the theta and gamma frequency range on WM performance. This effect decreases as a function of LEDD, a proxy for disease progression and is independent from motor performance.
LBA-23: Plasma markers of caffeine exposure but not of GCase activity are associated with resistance to Parkinson’s disease among GBA mutation carriers: a metabolomics-based analysis of PPMI


Objective: To validate and explore metabolomics-based plasma biomarkers of Parkinson’s disease (PD) resistance among GBA and LRRK2 mutation carriers and non-carriers.

Background: GBA and LRRK2 mutations are major risk factors for PD, although most who have them never develop PD. Identification of metabolic and metabolomic markers of PD despite such mutations will inform research on disease-modifying therapies and aid clinical trial design. Prior metabolomics of LRRK2 Cohort Consortium samples identified caffeine-related analytes as strong discriminants of PD status.

Method: Plasma samples from 629 Parkinson’s Progression Markers Initiative (PPMI) participants who comprised six main subgroups based on PD status (+/-) and genetic status (a GBA or LRRK2 mutation or neither) were analyzed by liquid chromatography coupled to mass spectrometry and by GCase enzyme activity using 4-MUG as substrate. Normalized analyte and activity levels were compared between groups using robust ANCOVA models for log2 analyte level as the dependent variable and age, sex, PD status, genetic status, levodopa use, and their interactions as independent variables. Unadjusted p-values are reported for pre-specified hypotheses.

Results: Among quantified targeted plasma analytes, 298 met reporting criteria. Caffeine and its main metabolite, paraxanthine, distinguished PD+ from PD- participants more than any other analyte (except for levodopa metabolites) with their levels 44% (p<1x10^-5) and 43% (p<1x10^-5) lower in PD, respectively. The reductions were similar for each genetic subgroup, including in GBA mutation carriers (n=164, 82 PD+ and 82 PD-), with caffeine and paraxanthine levels lower in PD by 46% (p=0.011) and 54% (p=2x10^-5), respectively. In contrast, GCase activity and GlcSph levels were 21% and 22% lower (p<1x10^-5) and 55% and 46% higher (p<1x10^-5) among GBA mutation carriers compared to non-carriers and LRRK2 mutation carriers respectively, but did not differ by PD status overall or among GBA mutation carriers specifically.

Conclusion: Metabolomics-based analysis of PPMI plasma showed caffeine-related analytes help discriminate PD+ from PD-, irrespective of genetic status, whereas markedly lower GCase activity and higher GlcSph characteristic of GBA mutation carriers were independent of PD status. These findings together with the lower PD risk among users of caffeine, its well-established neuroprotective properties in animal models, and its safety, support its candidacy for prevention trials in people at-risk for PD.

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LBA-24: Diagnostic yield of Next Generation Sequencing techniques in a movement disorders center in Chile

P. Saffie, A. Schuh, D. Muñoz, J. Fernández, F. Canals, P. Chaná-Cuevas (Chile)

Objective: Establish the diagnostic yield of genetic testing in a Latin American movement disorders center

Background: The needs of Latin America's countries are unmet in terms of registry of cases of genetic disorders, access to genetic studies, availability of medical staff trained in genetic counseling, and awareness of health professionals about such conditions. These problems make it challenging to research hereditary movement disorders and hinder the possibility of molecular diagnosis, genetic counseling, and the implementation of new therapeutics. Commercial laboratories have been offering genetic tests in Chile for approximately five years, but at a high cost and not covered by the health system or insurance companies. This study aims to describe the genetic findings of NGS techniques from the date that they became widely available in Chile.

Method: We obtained all the genetic reports of NGS panels and WES studies requested by CETRAM (the largest Movement Disorder clinic in the country) from May 2018 to May 2022. Medical records were screened and data collected in a structured template including age of onset, gender, pattern of inheritance, phenotype, and city of origin. Phenotypes were grouped by categories for data analysis, which was done descriptively. Diagnostic yield was calculated as the percentage of patients with pathogenic or like pathogenic mutations.

Results: In four years, 78 genetic tests (60% from patients from Santiago, and 40% from other places) were performed; 26 WES and 52 gene panels (ALS/DFT, Dystonia, HSP, Leukodystrophies, NBIA, Parkinson Disease and Prion Disease). Of them, 77% were for Parkinson Disease (n=15) and dystonia (n=25) genes and only 2 pathogenic mutations were found for each one of these groups. Most WES studies (80%) were indicated for ataxic syndromes, with a diagnostic yield of 23%. For all the cohort diagnostic yield was 18% (23% for WES and 15% for gene panels). One pathogenic mutation was found in CAMTA1, LRRK2, KMT2B, SGCE, chr18p, PIK3R, PRKN, PANK2, KCND3, KIAA0586; two in PRNP; and one likely pathogenic in TPP1 and ATP13A2 genes. On the other hand, 26% were reported as variants of unknown significance, and 56% of the results were negative. Results are summarized in table 1, and figure 1.

Conclusion: Of the population studied only 18% had positive results, despite that 47% had positive family history for inherited movement disorders, and 26% had VUS. An important number of Chilean patients are neglected as there isn't coverage by the health system (54% in recessive ataxias in CETRAM, Gama et al. 2022).

More resources are needed to expand the access to genetic testing and knowledge in this area, especially for providing genetic counseling and molecular diagnose. As most genetic research to date
has excluded non-Europeans, it is difficult to interpret variants of unknown significance, because most of them are reported for the first time.

![Graph](Image here)

**Figure 1. Genetic results by clinical group**
LBA-25: Increased phospho-AKT in blood cells from LRRK2 G2019S mutation carriers


Objective: To investigate whether differential phosphorylation states of blood markers can identify LRRK2 Parkinson’s disease (PD) patients.

Background: LRRK2-associated PD (L2PD), is the most frequent form of monogenic PD, and has a clinicopathological phenotype similar to idiopathic PD. Non-manifesting LRRK2 mutation carriers (L2NMC) are at high risk of PD but predicting the disease is challenging given the low penetrance and the lack of biomarkers.

Phospho-protein differences related to common LRRK2 mutations such as G2019S could act as progression or drug response biomarkers for L2NMC and L2PD. Levels of P-Ser-935-LRRK2 have been described in L2PD patients’ blood compared to L2NMC, and represent candidate biomarkers for target

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**Table 1. Summary of NGS studies performed by clinical subgroups of the cohort**

<table>
<thead>
<tr>
<th></th>
<th>Gene panel</th>
<th>Whole exome sequencing</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>52</td>
<td>26</td>
</tr>
<tr>
<td>Age of onset (mean (SD))</td>
<td>36.04 (23.10)</td>
<td>32.77 (19.68)</td>
</tr>
<tr>
<td>Gender = Male (%)</td>
<td>20 (38.5)</td>
<td>14 (53.8)</td>
</tr>
<tr>
<td>Inheritance (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominant</td>
<td>21 (40.4)</td>
<td>3 (11.5)</td>
</tr>
<tr>
<td>Recessive</td>
<td>2 (3.8)</td>
<td>10 (38.5)</td>
</tr>
<tr>
<td>Sporadic</td>
<td>29 (55.8)</td>
<td>13 (50.0)</td>
</tr>
<tr>
<td>Clinical group (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined ataxia</td>
<td>1 (1.9)</td>
<td>15 (57.7)</td>
</tr>
<tr>
<td>Combined Dystonia</td>
<td>6 (11.5)</td>
<td>1 (3.8)</td>
</tr>
<tr>
<td>Combined Parkinsonism</td>
<td>6 (11.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Dementia</td>
<td>1 (1.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Dystonia</td>
<td>14 (26.9)</td>
<td>1 (3.8)</td>
</tr>
<tr>
<td>Hereditary spastic paraparesis</td>
<td>5 (9.6)</td>
<td>1 (3.8)</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>13 (25.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Paroxysmal dyskinesia</td>
<td>1 (1.9)</td>
<td>2 (7.7)</td>
</tr>
<tr>
<td>Pure ataxia</td>
<td>1 (1.9)</td>
<td>6 (23.1)</td>
</tr>
<tr>
<td>Tremor</td>
<td>4 (7.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Origin = Not capital city (%)</td>
<td>16 (30.8)</td>
<td>16 (61.5)</td>
</tr>
</tbody>
</table>
engagement in LRRK2 inhibitor clinical trials. P-Ser-473-AKT has also been proposed as an LRRK2 phosphorylation substrate in PD animal models and LRRK2-PD iPSC-derived neurons.

Method: In this study, we expanded biomarker research in G2019S mutation carriers from PD by analysing the endogenous levels of P-Ser-935-LRRK2, P-Ser-1292-LRRK2, and P-Ser-473-AKT in peripheral blood mononuclear cells (PBMCs) from a large Spanish LRRK2 cohort (n=111) encompassing G2019S L2PD patients, PD at-risk G2019S L2NMC, iPD patients, and controls. To further assess the potential direct effects of G2019S on P-Ser-935-LRRK2 and P-Ser-473-AKT, we collected fresh PBMC lysates from additional subjects (n=11), including heterozygous and homozygous G2019S L2PD patients, heterozygous R1441G L2PD, and controls. We treated these samples with the 3-(4-Pyrimidinyl) Indazole (MLI-2), a potent and selective LRRK2 inhibitor that reduces its kinase activity.

Results: We found no differences at P-Ser-935-LRRK2 between groups but detected a specific increase of P-Ser-473-AKT levels in all G2019S carriers, either L2PD or L2NMC, absent in iPD.

Conclusion: Although insensitive to LRRK2 inhibition, our study identifies P-Ser-473-AKT as an endogenous candidate biomarker for peripheral inflammation in G2019S carriers using accessible blood cells.

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**LBA-26: Improving dysphagia in MSA and PSP with EMST – an Interventional Study**

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Objective: The objective of this study was to investigate whether a two-week-course of expiratory muscle strength training (EMST) improves dysphagia in patients with MSA and PSP, as observed in PD.

Background: Dysphagia is a major clinical concern in both in Multiple System Atrophy (MSA) and Progressive Supranuclear Palsy (PSP), occurring in up to 73% of patients. It is associated with malnutrition, dehydration, aspiration pneumonia and overall shorter survival. So far evidence-based treatment for dysphagia in MSA and PSP is lacking. Expiratory Muscle Strength Training (EMST) has proven to improve swallowing function and efficacy in a variety of neurological conditions. Until today, only two randomized, placebo-controlled studies have shown efficacy of EMST on swallowing reliability and efficiency in Parkinson’s disease (PD). Our double-blind placebo-controlled study on EMST in PD-associated dysphagia by Claus et al. showed improvement of endoscopic dysphagia scores regarding pharyngeal residue only in the intervention group, mirroring the positive effect of improved pharyngeal muscles strength during swallowing on dysphagia. In addition, previous studies from our group have shown phenotypical overlap of dysphagia patterns in PD and MSA, with both PD- and MSA-associated dysphagia exhibiting pharyngeal residue in about 50%. These results warrant exploring an intervention with EMST on dysphagia in MSA and PSP.

Method: In this open-label interventional trial (NCT05139342), patients with MSA and PSP were included if flexible endoscopic evaluation of swallowing (FEES) as part of the routine diagnostic work up revealed dysphagia. Dysphagia was assessed using the validated endoscopic 108-point dysphagia-score, rating premature spillage, penetration/aspiration, and residues with 3 swallows of semi-liquid, semi-solid and solid food consistencies. Higher scores indicate worse swallowing function. When dysphagia was detected, patients underwent a two-week-course of EMST, utilizing a calibrated handheld device (EMST; Aspire Products, Gainesville, FL) with a 1-way spring-loaded valve and an adjustable spring producing the most sufficient expiratory pressure to mechanically overload the expiratory and submental muscles. Devices were individually adjusted to 75% of the patient’s maximum expiratory pressure for subsequent training. During the two-week-intervention, patients followed the previously published standard EMST protocol, consisting of 5 sets of 5 repetitions per day. After the intervention, FEES was performed again, and outcome parameters compared to the initial endoscopic assessment.

Results: We here present data from 8 patients with MSA (4 female, median age 66 years [62 - 70], median disease duration 4 years [3 - 5]; 1 MSA-C/7 MSA-P) and 9 patients with PSP (4 female, median age 73 years [73 - 74], median disease duration 3 years [2 - 4]; 6 PSP-Richardson Syndrome, 1 PSP-Parkinsonism, 1 PSP-pure akinesia with gait freezing, 1 PSP-corticobasal syndrome).

Before the intervention, MSA patients scored 26.50±0.12 (mean±SE) points, indicating relevant dysphagia. After EMST, dysphagia-scores significantly improved by 10.38±0.16 points (39.2%; p<0.05). The main impact in the MSA cohort was observed on pharyngeal residue, which improved by 6.13±0.08 points (42.6%; p<0.01). A trend was observed for premature spillage (28.4%, p=0.08) and penetration/aspiration (33.3%; p=0.09; Fig.1A).

PSP patients scored 22.78±0.28 points before EMST, also indicating significantly impaired swallowing function. After the intervention, dysphagia-scores significantly improved by 4.67±0.09 points (20.5%; p<0.05). In the PSP cohort, the greatest improvement was observed for penetration/aspiration with a 56.3% improvement (p<0.05). A trend was observed for premature spillage, which improved by
Conclusion: Our results for the first time show a positive effect of a therapeutic intervention on dysphagia in patients with MSA and PSP. Our study indicates improvement of swallowing reliability and efficiency in both diseases. By reducing dysphagia in atypical Parkinsonian Syndromes, a major contributor to reduced quality of life and shorter survival is being addressed. To support these results, data will have to be collected in larger cohorts.

Disclosure: None of the authors report any conflicts of interest regarding the presented study.

LBA-27: Identifying progressive supranuclear palsy imaging subtypes using unsupervised machine learning


Objective: To understand the pathological and phenotypic heterogeneity of PSP, and the links between the two, we applied a novel unsupervised machine learning algorithm (SuStaIn) to a large cohort of...
Background: The degenerative 4-repeat tauopathy of PSP shows considerable heterogeneity in both the severity and neuroanatomical distribution of pathology at post-mortem. There is also marked variability in the rate of progression and the range of clinical presentations involving language, behaviour, and movement disorders. Although the most common clinical phenotype of PSP is Richardson syndrome (PSP-RS), variant clinical phenotypes (vPSP) may account for up to 50% of cases with PSP pathology. This clinical heterogeneity has implications for clinical trials, given that the PSP-subcortical variants have better survival (PSP-parkinsonism [PSP-P] 9 years, PSP-progressive gait freezing [PSP-PGF] 13 years vs PSP-RS 6-7 years) and slower rates of disease progression. Developing individualised disease progression models of pathological brain changes in PSP that predict this clinical heterogeneity will be essential to the success of future therapeutic trials. Subtype and Stage Inference (SuStaIn)7, a recently developed unsupervised machine learning algorithm that identifies groups of individuals with distinct biomarker progression patterns, is ideally suited to untangling the temporal and phenotypic heterogeneity of PSP.

Method: We applied SuStaIn to a large MRI dataset of PSP, to characterise spatiotemporal patterns of regional atrophy independent of PSP clinical phenotype. Our cohort comprised 426 PSP cases of which 367 had at least one follow-up scan, and 290 controls. Of PSP cases 357 were clinically diagnosed with PSP-RS, 52 with a PSP-cortical variant (PSP-frontal, PSP speech/language, or PSP-corticobasal), and 17 with a subcortical variant (PSP-parkinsonism or PSP-progressive gait freezing). The model was fit using volumetric MRI features extracted from baseline structural (T1-weighted) MRI scans and the trained model then used to subtype and stage follow-up scans. This information was used to validate the longitudinal consistency of subtype and stage assignments. We further compared the clinical phenotypes of each subtype to gain insight into the relationship between PSP pathology, atrophy patterns, and clinical presentation.

Results: The data supported two subtypes with distinct progression of atrophy: a Subcortical subtype, in which early atrophy was most prominent in the brainstem, ventral diencephalon, superior cerebellar peduncles and the dentate nucleus; and a Cortical subtype, in which there was early atrophy in the frontal lobes and the insula alongside brainstem atrophy. There was a strong association between clinical diagnosis and SuStaIn subtype with 82% of PSP-SC cases and 81% of PSP-RS cases assigned to the Subcortical subtype and 82% of PSP-C cases assigned to the Cortical subtype. The subtypes converged to a similar pattern of end-stage atrophy. Increasing stage was associated with worsening clinical scores, while the Subcortical subtype was associated with worse clinical severity scores compared to the Cortical subtype (PSP rating scale and Unified Parkinson’s Disease Rating Scale). Validation experiments showed that subtype assignment was longitudinally stable (95% of scans were assigned to the same subtype at follow-up) and individual staging was longitudinally consistent with 90% staying at same stage or progressed to a later stage at follow-up.

Conclusion: We applied SuStaIn, an unsupervised machine-learning algorithm, to structural MRI data to identify 2 distinct progressive subtypes of spatiotemporal atrophy in PSP. These image-based subtypes are differentially enriched for PSP clinical syndromes and show different clinical characteristics, providing insights into the relationship between PSP pathology and clinical syndrome. Being able to
Longitudinal clinical decline and baseline predictors in progressive supranuclear palsy


Objective: To assess the evolution of these core clinical features across variants and assess baseline clinical and neuroimaging predictors of progression.

Background: Progressive supranuclear palsy (PSP) is associated with several clinical variants defined based on ocular motor dysfunction, postural instability, akinesia, and cognitive dysfunction, although little is known about how these features progress over time.

Method: Ninety-three PSP patients were recruited by the Neurodegenerative Research Group, Mayo Clinic, and underwent two visits 1-year apart, with baseline MRI and [18]flortaucipir PET. We compared baseline and annualized rates of clinical change on the PSP Rating Scale (total, ocular motor, gait/midline scores) and Montreal Cognitive Assessment, across PSP-Richardson’s, PSP-cortical and PSP-subcortical variants and assessed relationships between rates of change and baseline regional imaging.
Results: Ocular motor scores differed across groups at baseline and follow-up, with lowest scores observed in PSP-subcortical, but no differences were observed in rate of change. Rates of change in PSP Rating Scale total and gait/midline scores differed across groups, with PSP-subcortical showing the slowest progression. Follow-up PSP Rating Scale total was lowest in PSP-subcortical. Greatest cognitive impairment was observed in PSP-Cortical. Sample size estimates for treatment trials differed across PSP variants. Greater baseline flortaucipir uptake in midbrain and motor cortex correlated with faster rates of clinical decline.

Conclusion: The PSP Rating Scale and its subscores might be useful markers for the prognostic stratification of PSP variants. Imaging of the motor cortex and midbrain may help predict rate of decline.