3D Fusion imaging of transcranial ultrasound and quantitative MRI for investigating the microstructure of substantia nigra hyperechogenicity in Parkinson’s disease

Lucas Nürnberger, Simon Baudrexel, Uwe Walter, Rüdiger Hilker, Velizar Kolev, Georgios Sakas

Department of Neurology, University Hospital Frankfurt; Brain Imaging Center Goethe University Frankfurt; MedCom GmbH, Darmstadt
Frankfurt, Germany

Objective: The aim of this work was to set up a procedure allowing reliable fusion of 3D images from transcranial ultrasound (TCS) and quantitative MRI (qMRI) in order to determine T1 and T2* relaxation times in abnormally hyperechogenic brain structures in parkinsonian syndroms. The procedure was applied in a pilot study investigating substantia nigra (SN) hyperechogenicity in idiopathic Parkinson’s disease (PD) and spatial accuracy was assessed for several landmarks.

Background: 2D TCS has become an established tool supporting early diagnosis of PD. Diagnostic criteria are characteristic echogenic enlargement and increased intensity of the SN in the transversal plane (=SN hyperechogenicity). Histopathological post mortem studies and animal models suggest gliotic processes and iron accumulation to contribute to this increased echogenicity, but it is still unclear whether these assumptions also apply for the clinically observed SN hyperechogenicity in patients with early PD. At this point, qMRI parameters could provide valuable insights into the underlying microstructural tissue changes. However, a combined 3D TCS and qMRI analysis of SN hyperechogenicity in PD has not been performed yet and no standard procedure exists for 3D fusion of both image modalities.

Methods: 19 PD patients with lateralized motor symptoms and SN hyperechogenicity (HY I-II, 60.0 ± 10.4 years, 7 female ) and 14 healthy subjects (66.8 ± 8.3, 8 female) underwent anatomical MRI (1x1x1 mm3), quantitative T1- and T2*-mapping (Preibisch and Deichmann 2009, Baudrexel et al. 2009) and real-time 3D ultrasound fusion imaging (Virtual Navigator, MedCom; MyLAB Twice, Esaote). The brainstem side contralateral to the more (less) severe motor symptoms was defined as the more (less) affected brainstem side MABS (LABS). 3D fusion of midbrain TCS and MRI was achieved according to the following steps: 1. Identification of a set of 9 surface markers on the subject’s lateral orbita borders, nasal root, tip and bridge and anterior ear helices using the ultrasound probe. 2. Identification of the corresponding points in the anatomical MRI enabling automatic registration. 3. Registration was improved by a subsequent manual fine tuning (real-time) to correct for spatial deviations of midbrain, 3rd ventricle, aqueduct and posterior cerebral arteries. 4. Recording of 3D ultrasound brainstem images with second harmonic imaging by placing the probe on the transtemporal bone window and tilting the probe through the entire midbrain from the top of the 3rd ventricle to the pons. Images were saved in the MRI space. 5. Spatial registration was further optimized offline using rotate- and in-plane-movement functions implemented in Virtual Navigator. Finally, volume-of-interests (VOI) of the midbrain, the 3rd ventricle and the aqueduct were manually drawn on transversal layers of 3D ultrasound images and spatial discrepancies of their outlines between anatomical MRI and 3D ultrasound were measured. Analogously drawn VOIs of SN (hyper)echogenicity (see Fig. 1) were co-registered on the quantitative T1- and T2*-maps using FSL (see Fig. 2) and the respective T1 and T2* values were evaluated using a custom build MATLAB script.

Results: Spatial overlap of fusion imaging was clearly improved when combining automatic registration and real-time fine tuning with an additional offline correction for linear and rotational displacement errors (see Fig. 3). Mean displacement of midbrain outlines, 3rd ventricle, Z-axis and aqueduct was 1.4 ± 0.5 mm / maximum 2mm (compared to 4.1 mm ± 1.5 mm / max. 8 mm with automatic registration alone). The volume of the SN hyperechogenicity was larger at the MABS (0.54 ± 0.14 cm3) as compared to the LABS (0.40 ± 0.10 cm3, p=0.028, paired t-test) and to controls (0.39 ± 0.1 cm3, p=0.007, volumes of both sides averaged). Median T1 values of the SN hyperechogenicities were lower as compared to healthy controls at the MABS (MABS vs. controls: median T1 = 1023.1 ± 59.5 ms vs. 1067.0 ± 54.3 ms, p=0.046), whereas only a tendency towards lower T1 values was observed...
for the LABS (1042.3 ± 76.2 ms, p = 0.33). In contrast, no significant T2*-changes could be detected between the groups.

**Figure 1:** Manual segmentation of substantia nigra (SN) hyperechogenicity as a 3D volume-of-interest (VOI)

Top row: Outlines of SN-related hyperechogenic midbrain tissue were traced manually in each transverse plane (A) of the 3D ultrasound image. Coronal (B) and sagittal (C) views of the resulting VOI are displayed.

Bottom row: Projection of the resulting 3D ultrasound-based VOI into anatomical MRI

**Figure 2:** T1 and T2* maps for investigating the microstructure of substantia nigra (SN) hyperechogenicity (sample patient)

Ultrasound-defined SN hyperechogenicity volume-of-interests (VOIs) of the more (yellow) and less (pink) affected brainstem side were coregistered on the T1 (top row) and T2* map (bottom row) for extracting the underlying relaxation times. The midbrain VOI (red) was also coregistered to recognize major spatial discrepancies between ultrasound and qMRI.
Conclusions: An innovative procedure was developed allowing projection of the SN (hyper)echogenicity as a 3D ultrasound-defined VOI into MRI space for evaluation of underlying T1 and T2* relaxation times. However, additional post processing correcting for linear and rotational displacement errors was required for a close overlap of the two image modalities. Therefore, spatial accuracy is still a critical limitation of this method and needs further improvement. The observed T1 decrease in absence of a significant T2* decrease within the hyperechogenic SN volume of PD patients may rather indicate T1 shortening gliotic processes than iron accumulation, as iron in principle shortens both T1 and T2*. Alternatively, a significant T2* decrease of present iron accumulation was not detected due to methodological problems, as involuntary movements during MRI acquisition have larger confounding effects on T2* than on T1 mapping.

LBA 02
RAB32 as a cause of familial Parkinson’s disease

Emil Gustavsson, Jordan Follett, Castel Miguel Ramirez, Joanne Trinh, Jesse Fox, Jan Aasly, Emmanuelle Pourcher, Faycel Hentati, Matthew Farrer

University of British Columbia; Norwegian University of Science and Technology and St. Olav’s Hospital; Shepherd Medical Center; Mongi Ben Hamida National Institute of neurology
Vancouver, BC, Canada; Trondheim, Norway; QC, Canada; Tunis, Tunisia

Objective: To investigate the role of genetic variability in the Rab GTPase family of genes in familial Parkinson’s disease (PD).

Background: Rab GTPases constitute the largest family of small GTPases, localizes to distinct intracellular membranes, and function as molecular switches that alternate between two conformational states: the GTP-bound ‘on’ form and the GDP-bound ‘off’ form. Rab32 localizes to the mitochondria-associated membranes (MAM), a
region formed between mitochondria and a specialized subdomain of the endoplasmic reticulum (ER) with a particular lipid and protein composition that is involved in the crosstalk with mitochondria. Cellular processes such as autophagy, mitochondrial dynamics, phagocytosis or inflammatory processes in the brain have previously been linked to RAB32. It has been demonstrated that RAB32 directly interacts with LRRK2, and they co-localize at recycling endosomes and transport vesicles. Thus, RAB32 may regulate the physiological functions of LRRK2.

Methods: We studied 131 families with multi-incident parkinsonism. Whole exome sequencing (WES) and further validation and segregation analysis was done by means of Sanger sequencing in probands and additional family members. We then performed immunohistochemistry (IHC) analysis in striatal and mid-brain sections from LRRK2 p.G2019S knock-in mice. We have generated a V5 tagged WT and p.S71R RAB32 construct and will assess phosphorylation in neuronal cultures. Additionally, we are assessing whether co-localization of RAB32 with LRRK2 is altered as an outcome of RAB32 p.S71R and/or LRRK2 p.G2019S.

Results: Through WES we found a total of 18 variants across 17 different RABs. Further sequencing of additional family members and segregation analysis identified RAB32 p.S71R to segregate with in autosomal dominant manner in three unrelated multi-incidental families of Tunisian and French Canadian origin albeit with incomplete penetrance. The mutation at S71 occurs at highly conserved phosphorylation site in RAB32. Through IHC analysis of tissues from LRRK2 p.G2019S knock-in mice we observe a clear expression in TH-expressing nigrostriatal neurons. Although preliminary, this expression is seemingly reduced in an allele dependent manner with the presence of p.G2019S.

Conclusions: Our data suggest that a novel mutation in RAB32 (p.S71R) causes late-onset autosomal dominant PD. RAB32 is expressed in the site of lesion for PD and this expression is seemingly reduced as a consequence of LRRK2 p.G2019S. We hypothesize that RAB32 p.S71R ablates phosphorylation by LRRK2 and hence, links LRRK2 and RAB32 in the pathogenesis of PD.

LBA 03
Objective Data in Parkinson’s disease: A description of over 10,000 Parkinson’s disease symptom scores across the world using the Personal KinetiGraph (PKG)

Peter Lynch, Rajesh Pahwa, Filip Bergquist, Malcolm Horne

Global Kinetics Corp; University of Kansas Medical Center; University of Gothenburg; Florey Institute for Neuroscience and Mental Health, University of Melbourne; Centre for Clinical Neurosciences and Neurological Research, St Vincent's Hospital
Minneapolis, MN, USA; Kansas City, KS, USA; Göteborg, Sweden; Parkville, Victoria, Australia; Fitzroy, Victoria, Australia

Objective: The objective was to describe the symptomology scores from a large deidentified database of PD patients using the PKG.

Background: The Personal KinetiGraph™ (PKG™) Movement Recording System provides continuous, objective, ambulatory movement data during routine daily activities and provides information on medication compliance, motor fluctuations, immobility, and tremor for patients with Parkinson’s Disease (PD). Previous validation studies have correlated PKG objective scores with other standard PD methods of symptom capture (e.g. Unified Parkinson’s Disease Rating Scale [UPDRS], Abnormal Involuntary Movement Scale [AIMS], etc.).

Methods: 10,148 complete and deidentified PKG reports from Jan 2012 to Jan 2017 used globally for routine clinical care were included. Scores for Bradykinesia (BKS), Dyskinesia (DKS), Fluctuations (FDS), Percent Time Immobile (PTI: sleep), Percent Time with Tremor (PTT) were analyzed. Various sub-analyses were performed and are ongoing. Any incomplete records (e.g. wear time not > 4 days) were excluded.

Results: Globally, the mean BKS score was 26.4 and the median BKS was 25.8. 65% of patient BKS scores were >23 (correlates with UPDRS III score of approximately 21), 52% of BKS scores were >25 (~27 UPDRS III), and 32% were >29 (~42 UPDRS III). The mean DKS was 4.4 and the median DKS was 1.9 globally. 16% of DKS
scores were >7 (~7 mAIMS), and 12% were >9 (~10 mAIMS), on a global basis. 34% of PTI scores were above 10%. 50% of PTT scores were above 1%. Symptom scores across different geographic regions showed some variation.

Conclusions: This analysis describes Parkinson’s symptomology across a large number of patients. It also suggests that a large proportion of PD patients have sub-optimal scores. Like other diseases, objectively tracking symptoms over time & developing treatment targets could help improve symptom control of PD patients.

LBA 04
PAR polymer concentration may serve as a marker of Parkinson’s disease (PD) diagnosis and PD-related cognitive decline


Department of Neurology, Johns Hopkins School of Medicine; Neurodegeneration and Stem Cell Programs, Institute for Cell Engineering, Johns Hopkins University School of Medicine; Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health; Department of Pathology, Stanford University School of Medicine, Veterans Affairs Puget Sound Health Care System, Department of Neurology University of Washington School of Medicine, Department of Epidemiology, University of California, Irvine, School of Medicine

Baltimore, MD, USA; Palo Alto, CA, USA; Seattle, WA, USA; Irvine, CA, USA

Objective: To determine if poly (ADP-ribose) (PAR) polymer concentration in the cerebrospinal fluid is diagnostic of Parkinson’s disease (PD) and PD-related cognitive decline.

Background: Activation of the PAR polymer is both necessary and sufficient for regulated cell death of neurons. The PAR cell death cascade, called parthanatos, has been implicated in the death of the substantia nigra neurons that cause the motor symptoms of PD.

Methods: Participants at the Johns Hopkins University site of the NINDS Parkinson’s Disease Biomarker Program (PDBP) underwent extensive clinical and cognitive testing and a lumbar puncture annually. The cerebrospinal fluid (CSF) was centrifuged, aliquoted, and stored at -80 degree Celsius within one hour of acquisition. 100 µL of thawed CSF was used to determine PAR concentrations by a sandwich ELISA assay for PAR. Student’s t-test were used to compare the concentration of PAR between controls and individuals with PD and those with normal cognition and cognitive impairment. A generalized linear model then evaluated the determinants of change in PAR concentration and whether PAR concentration was associated with cognitive changes.

Results: One hundred ten individuals contributed CSF at baseline (80 PD, 30 control), 94 individuals contributed CSF at the first follow-up (68 PD, 26 controls), 71 individuals contributed CSF at the second follow-up (51 PD, 20 controls), and 36 individuals contributed CSF at the third follow-up (28 PD, 8 controls). At baseline, the average age for both PD and controls was approximately 66 years (p=0.71) and 67% of PD patients were men while 37% of controls were men (p<0.01). Mean PD duration was 6.7 years. There were differences in the mean concentration of PAR between individuals with PD and controls at the first three visits, with a trend toward a difference in the 4th visit (visit 1: PD mean 112.13, control mean 87.99 p=0.04; visit 2: PD mean 145.49, control mean 110.63 p=0.04; visit 3: PD mean 132.29, control mean 86.06 p=0.01; visit 4: PD mean 151.88, control mean 111.07 p=0.08). Disease status was a significant predictors of PAR concentration (p<0.01), even after controlling for age, gender, MDS-UPDRS Motor scores, levodopa equivalent dosing, and cognitive impairment. PAR concentration at visit 2 and visit 4 were significantly different from PAR concentration at visit 1 (p<0.01, p=0.01) Among only PD participants, PAR concentration (p=0.03) and MDS-UPDRS Motor scores (p<0.01) were significant predictors of cognitive decline.

Conclusions: Concentration of PAR polymer in the CSF was different between PD and control participants over a 3-year follow up period, and cognitive status was a significant predictor of PAR polymer concentration among the PD participants. PAR polymer concentration in the CSF may serve as a marker for PD and may predict cognitive
decline. Further longitudinal follow up of our cohort and testing in other cohorts are required to validate these findings.

LBA 05
The Genetic Architecture of Neurodegenerative Diseases in the Johns Hopkins Brain Bank


Neurodegenerative Diseases Research Unit | NINDS | National Institutes of Health, Bethesda, MD, USA; Laboratory of Neurogenetics, National Institute of Ageing, Bethesda, MD, USA; Dept. of Neurology, Johns Hopkins University, Baltimore, MD, USA; Dept. of Pathology, Johns Hopkins University, Baltimore, MD, USA

Objective: To determine the genetic profile of neurodegenerative diseases in the Johns Hopkins brain bank and to determine genotype-phenotype correlations.

Background: Over the last two decades an increasing number of causative mutations and genetic risk variants have been implicated in the pathogenesis of neurodegenerative diseases. The ability to rapidly screen for such disease-associated variants using custom-designed, high-throughput genotyping arrays provides new opportunities for molecular research and clinical diagnostics.

Methods: We performed NeuroChip genotyping in 1,243 neurodegenerative disease cases from the Johns Hopkins Brain Bank (comprising all neurodegenerative disease cases), 108 normal controls, and 27 vascular dementia cases to examine genotype-phenotype correlations. The NeuroChip is a custom-designed genotyping platform for rapid, high-throughput and affordable screening of disease-associated genetic variants. A total of 1,361 samples that passed quality control were examined for pathogenic mutations, likely pathogenic variants and high-risk variants.

Results: We identified pathogenic mutations in LRRK2, GBA, APP, PSEN1, GRN, C9orf72, SETX, SPAST, and CSF1R, as well as high-risk variants in APOE, GBA, TREM2 and MAPT. Here, we describe the clinical and pathological phenotypes of mutations carriers and high-risk variants.

Conclusions: NeuroChip is a cheap method for high-throughput screening of samples with neurodegenerative diseases. We were able to identify a molecular cause in several cases with unclassified neurodegenerative syndromes, highlighting the diagnostic utility of this affordable screening tool.

LBA 06
Spinal cord stimulation improves antecipatory postural adjustment and freezing of gait in Parkinson disease in chronic implanted STN-DBS patients: Preliminary Data

Carolina Souza, Carolina Oliveira Souza, Andrea Pardini, Daniel Coelho, Luís Augusto Texeira, Erich Fonoff

University of São Paulo, Brazil
São Paulo, Brazil

Objective: To evaluate the effects of Spinal cord stimulation (SCS) over the Anticipatory postural adjustment (APA) measurements in PD patients and its correlation to gait improvement.

Background: Gait disturbances and freezing of gait (FoG) are common in late Parkinson’s disease (PD), often leading to loss of independence and increasing morbidity. A recent pilot study suggested positive effects of spinal cord stimulation (SCS) in PD patients previously treated with DBS. Despite the encouraging clinical results, no mechanistic approach was investigated at the initial trial. Anticipatory postural adjustment (APA) is an essential aspect of postural control required for starting any successful voluntary movement. APA combines motor and
cognitive components of movement preparation and has been thought to be controlled by cortical circuitry, involving the supplementary motor area (SMA) and prefrontal cortex. This is shortened during FOG in PD patients.

**Methods:** 4 PD patients with gait disorder and FoG, previously treated with STN DBS underwent evaluations in 3 conditions: SCS at 300 Hz, SCS at 60 Hz and SCS turned off. DBS was kept always on. We evaluated the SCS effects on APA and FoG. The biomechanical assessment comprised: 1) Force plate analysis during step initiation (3 trials) measuring the amplitude and time of APA (time between onset of APA and the step); 2) Accelerometry spectral analysis during 10m-walk test (3 trials) providing the percentage of FoG occurrence and trunk acceleration (Figure 1). Analysis: For each patient was calculated the average of 3 trials, so in each one the following calculations were made: 60-OFF/100 or 300-OFF/100, which is the gain of the condition (60Hz or 300Hz) in relation to OFF condition. For the group (N=4) a t-test was applied and a simple t-test contrasting 60 and 300Hz.

**Results:** FoG index was reduced in SCS 300Hz in relation to SCS Off and 60Hz stimulation (p<0.042), so patients had significantly less in freezing time while under SCS at 300Hz. APA time decreased in 300Hz condition comparing with OFF and 60 Hz conditions (p<0.041), suggesting better coupling between preparation and movement during step initiation.

**Conclusions:** 300 Hz SCS seems to improve gait by decreasing FoG and increasing the efficiency of the preparation and movement coupling during step initiation.
Glial Cell Line-Derived Neurotrophic Factor (GDNF): Indication of Biologically Mediated Clinical Benefit in Parkinson’s Disease After 80 Weeks of Treatment via Intermittent Intraputamenal Convection-Enhanced Delivery (CED)

The GDNF Study Group

North Bristol Trust, MedGenesis Therapeutix Inc, Renishaw, University of Cardiff, University of British Columbia, Bristol, UK; Victoria, Vancouver Island, Canada; Gloucestershire, United Kingdom; Cardiff, Wales; Vancouver, BC, Canada

Objective: Exploring the neurorestorative effect of GDNF after a total of 18 months of therapy.

Background: Our 9-month double blind investigation of monthly intraputamenal infusions of GDNF versus placebo, accepted to be presented at the 21st International Congress, failed to show significant improvement in OFF-state UPDRS motor score. That said, at the 40 week time-point all motor endpoints numerically fell in favour of GDNF, a post-hoc responder analysis was significantly in favour of GDNF and the GDNF group showed highly significantly increased 18F-DOPA uptake throughout the entire putamen that reached 100% improvement in the posterior portion. One possibility for the mismatch between our PET and clinical findings, is a lag during neurorestoration between clinical benefit versus PET-evidenced biological response, clinical benefit potentially requiring longer treatment exposure than 9 months. Here we present our now available extension study data post further 4 weekly putamenal infusions administered from the 9 to 18-month time point post baseline.

Methods: Following a single centre, 9-month, placebo-controlled double-blind study we conducted an open-label 40-week extension study (weeks 40-80) where all 41 subjects received 4-weekly bilateral intraputamenal GDNF infusions, administered via a skull mounted port, in a manner to achieve convection enhanced delivery (CED). Treatment allocations from the preceding double-blind parent study (1:1 randomization ratio) were not disclosed to patients or blinded raters.

Results: At the 18 month time point both groups (GDNF/GDNF and placebo/GDNF) showed moderate to large improvements over baseline in OFF-state UPDRS scores at Week 80 (motor: -9.6 vs. -9.0 points; ADL: -6.9 vs. -4.6 points). Week 80 results in the GDNF/GDNF group were significantly better than Week 40 results in the placebo group (motor: -9.6 vs. -3.8 points, p=0.0108; ADL: -6.9 vs. -1.0 points, p=0.0003). Size and dynamics of the effects of the first 40 weeks on GDNF in both groups were similar. The known correlation in OFF state UPDRS motor and ADL scores with putamenal 18F-DOPA uptake was discernable at baseline, mostly lost at Week 40, and re-established when comparing Week 80 clinical outcome with Week 40 PET results.

Conclusions: Despite obvious limitations due to the loss of our placebo group, with all subjects rolling over to active therapy after 9 months, the results of this extension study support the conclusion that 18 months administration of GDNF via 4 weekly intraputamenal CED provides substantial neurorestoration / neuroprotection sufficient to achieve significant biologically mediated clinical benefit to Parkinson’s patients. Prospective corroboration of our findings in a multi-center, randomized, double-blind study testing GDNF over 80 weeks and potentially including a higher dose level is warranted. 1) Randomized Parkinson’s Trial of GDNF Administered via Intermittent Intraputamenal Convection-Enhanced Delivery. The GDNF Study Group. The 21st International Congress of Parkinson’s Disease and Movement Disorders. Vancouver, June 4-8, 2017.
LBA 08
MoPED – Mortality and Co-Morbidities of a Large German Population of Patients with Parkinson’s Disease

Walter Maetzler, Gudula Petersen, Daniela Chase, Niklas Schmedt, Lennart Hickstein, Sebastian Heinzel, Daniela Berg, Volker Amelung

Department of Neurology, Christian-Albrechts-University; Grünenthal GmbH; INAV privates Institut für angewandte Versorgungsforschung GmbH; InGef - Institut für angewandte Gesundheitsforschung Berlin GmbH
Kiel, Germany

Objective: To compare mortality and co-morbidities of a representative population of patients with Parkinson’s disease (PD) in Germany with an age- and sex-matched control group.

Background: PD is a progressive disorder of the central nervous system leading to disability, care dependency, reduced quality of life and premature death. Mainly elderly persons are affected by PD and frequent co-morbidities lead to high number of co-medications.

Methods: The InGef research database contains anonymized patient-level claims data from German Statutory health insurances. For this cross-sectional analysis, a representative sample of approximately 4 million insured persons served as study population (4.5% of German population). PD patients were identified in 2015 based on ICD-10-GMcode G20.x. Frequency of co-morbidities and mortality in PD patients were compared to a control group without PD with the same age and gender profile as well as regional distribution in Germany.

Results: In total, 21,714 patients fulfilled the case definition of PD in 2015 with a mean age of 77.8 years and nearly equal number of females (49.2%) and males (50.8%). Overall, 10.7% of the PD patients died (N=2,330) compared to 5.8% of the control group (p<0.001). The mean number of physician contacts was higher in the PD group compared to the control group (15.2 vs. 12.2, p<0.001), same applied to the mean number of days in hospital (12.9 vs. 6.2, p<0.001). Certain co-morbidities were more frequent in the PD group compared to the control group, as for instance bladder dysfunction (46 vs. 22%, p<0.001), dementia (39 vs. 13%, p<0.001), depression (45 vs. 22%, p<0.001), and diabetes (35 vs. 31%, p<0.001).

Conclusions: In this large dataset from German Statutory health insurances, diagnosed PD was associated with presence of several co-morbidities, such as diabetes, and a nearly two-fold increase with regard to mortality. Longitudinal studies are warranted to further investigate predictors of mortality in PD patients and the impact of co-morbidities.

LBA 09
Simultaneous low frequency deep brain stimulation of the substantia nigra pars reticulata and high frequency stimulation of the subthalamic nucleus to treat l-dopa non responsive freezing of gait in Parkinson’s disease

Francesc Valldeoriola, Esteban Muñoz, Jordi Rumià, Pedro Roldán, Ana Cámara, Yaroslau Compta, Mª José Martí

Institut Clínic de Neurociències, Hospital Clínic de Barcelona, Universitat de Barcelona
Barcelona, Spain

Objective: To demonstrate that low frequency (63Hz) deep brain stimulation (DBS) of the substantia nigra pars reticulata (LF-SNr) combined with standard high frequency stimulation of the dorsolateral subthalamic nucleus (HF-STN) proves to be clinically relevant in the amelioration of freezing of gait that no longer improves with dopaminergic treatment in patients with advanced Parkinson’s disease (PD).

Background: Some patients with PD develop freezing of gait resistant to l-dopa treatment (so-called "on" freezing). STN-DBS has limited effect on these symptoms that do not with l-dopa therapy and, therefore, such patients are not considered to be good candidates for DBS surgery. Some previous reports suggested that gait disorders in PD could
be improved by low frequency stimulation of the most ventral areas of the STN, by stimulation of the SNr, and high frequency simultaneous stimulation of both nuclei. However, the results of these works were inconclusive.

**Methods:** This was a prospective, single-center, randomized controlled pilot trial. Six PD patients with “on freezing” were included. They underwent stereotactic surgery and a 8-contact lead, of the Vercise™ DBS system (Boston Scientific Corporation, Natick, MA) was implanted bilaterally in the STN-SNr. Three of the contacts were left in the SNr. This system is capable to deliver high and low frequencies at different electrodes at the same time. Patients received LF-SNr, HF-STN, or combined stimulation. All patients were stimulated with the three different programs (cross-over design) in a randomly assigned setting for two months each. Patients were evaluated by a rater, who was blinded to the stimulation program, using the Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) and the Tinetti Balance and Walking Assessing tool “off” and “on” medication, and the Freezing of Gait Questionnaire.

**Results:** Mean age of patients was 59.1 (43-70) years, and disease duration was 16.1(10-20) years, with 7.3 (3-15) years from the onset of “on freezing”. Mean equivalent l-dopa dose was 1250±427. All patients presented with motor fluctuations and dyskinesias. In off medication, the UPDRS II and III and Tinetti scores improved after surgery in the three different stimulation programs with respect to basal scores. However, the improvement was greater in patients receiving combined STN-SNr stimulation. Equivalent l-dopa dose was reduced by 63% after HF-STN, 43% after LF-SNr, and 53% after combined stimulation. The Freezing of Gait Questionnaire also showed clear improvement in its different items in five of the patients; combined stimulation globally achieved better results in four out of the six patients; these patients preferred combined stimulation at the end of the study and remained with combined stimulation after two years of follow-up. In three of them, freezing of gait almost completely disappeared (Figures 1 and 2). The other two patients presented better outcomes with HF-STN. Isolated SNr stimulation resulted in relative improvement of freezing, but the global antiparkinsonian effect was lower than with the other stimulation programs. LF-SNr produced transitory blurred vision in two patients, and no serious side effects were observed.

**Conclusions:** The effects of combined HF-STN and LF-SNr on the severity of gait disorders in PD are promising. Freezing markedly improved in five of the patients in spite of being considered poor candidates for DBS surgery due to the presence of gait problems unresponsive to dopaminergic therapies. Studies with higher number of patients are needed to define the role of combined stimulation in the treatment of “on” freezing.

**Freezing of gait questionnaire: presence of freezing**

![Freezing of gait questionnaire](image-url)
Clinical and genetic analysis of Spinocerebellar ataxias in Zambia

Masharip Atadzhanov, Danielle Smith, Mwila Mwaba, Omar Siddiqi, Jacquie Greenberg

University of Zambia; University of Cape Town, Cape Town, South Africa; Beth Israel Deaconess Medical Center, Boston, MA, USA
Lusaka, Zambia; Cape Town, South Africa; Boston, MA, USA

Objective: To represent the results of the first clinical and genetic analysis of four families with spinocerebellar ataxia (SCA) type 7 and three additional families with SCA in Zambia.

Background: To date, thirty seven types of SCAs, have been identified. A subset of the SCAs are caused by the pathogenic expansion of a CAG repeat tract within the corresponding gene. Ethnic and geographic differences are evident in the prevalence of dominant SCAs. Few studies on the clinical phenotype and molecular genetics of the SCAs are available from the African continent. Established studies mostly concern the South African populations, where there is a high frequency of SCA1 and SCA7. The SCA7 mutation in South Africa have been found almost exclusively in families of Black African ethnic origin.

Methods: The study was conducted at the University Teaching Hospital in Lusaka, Zambia. Ataxia was quantified with the Brief Ataxia Rating Scale derived from the modified international ataxia rating scale. Molecular genetic testing for 5 types of SCA (SCA1, 2, 3, 6 and 7) was performed at the National Health Laboratory Service at Groote Schuur Hospital and the Division of Human Genetics, University of Cape Town, South Africa. The clinical, molecular and radiological features were evaluated in seven families with autosomal dominant cerebellar ataxia. Haplotyping studies were performed to determine whether a common founder exists between South African and Zambian SCA7 families.

Results: All affected families were ethnic Zambians from different tribes (Bemba, Nyanja, Lozi), originating from different regions of the country (Eastern, Western and Central province). Four families, including a total of 33

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**Freezing of gait questionnaire: duration of freezing**

![Chart showing duration of freezing](chart.png)
affected individuals, had molecularly confirmed SCA7. The age–of-onset of the disease varied from 12 to 59 years. The main phenotype was characterized by gait and limbs ataxia, dysarthria, visual loss, ptosis, ophthalmoparesis/ophthalmoplegia, pyramidal tract signs and dementia. Affected members of the families had progressive macular degeneration and cerebellar atrophy. All families displayed marked anticipation of age at onset and rate of progression. The SCA7 CAG repeat ranges varied from 48 to 72 repeats. The haplotyping results suggested that the South African and Zambian SCA7 families tested share a common founder. Three additional families were found to have clinical phenotypes suspected of being SCA2, although DNA was not available for molecular confirmation. The age of onset of the disease in these families varied from 19 to 53 years. The most common clinical picture included a combination of cerebellar symptoms with slow saccadic eye movements, peripheral neuropathy, dementia and tremor.

Conclusions: SCA families have been identified in the ethnic Zambian population. The phenotypes in these families are similar to that described in the literature. The present study suggests that the SCA7 mutation in Zambian families may have originated in another African country. Our study demonstrates the importance of clinical and molecular investigations of the inherited ataxias and other neurodegenerative disorders in the ethnic Zambian population.

LBA 11
Impedance Variation Of Directional DBS Lead In Chronic Follow-Up Of Parkinsonian Patients

Roberto Eleopra, Sara Rinaldo, Manuela Pilleri

Neurological Unit, University Hospital S.Maria della Misericordia Udine and Neurology Functional Unit, Villa Margherita of Arcugnano (VI)
Udine and Arcugnano-Vicenza, Italy

Objective: The aim of this study is to evaluate the impedances variation measures in Parkinsonian subjects who underwent to DBS surgery with a new directional system capable of directional current steering.

Background: Deep Brain Stimulation of Subthalamic nucleus (STN) has been an effective treatment for Parkinson disease for years. In order to provide a proper therapeutic current one aspect that has to be taken into account is the control of the impedances fluctuations of the lead contacts. For this reason a current control DBS system with multiple power sources is useful to avoid any modification of the volume of tissue activated as a consequence of impedance modification, providing therapy stability. This topic became interesting in consideration of the recent availability of new directional DBS systems, in which the directional contacts along the lead have a lower surface (\[1.5\text{ mm}^2]\) respect to the standard cylindrical ring contacts (\[6\text{ mm}^2]\). The lower surface area of the contacts physiologically implicates an increment of the impedances values and a potential higher fluctuations.

Methods: 10 consecutive patients, with diagnosis of Parkinson’s disease, have been implanted since December 2015 in bilateral STN using a Directional DBS system (DB-2202 Cartesia leads connected to Vercise PC IPG, Boston Scientific-Valencia, California). During the activation visit and the following follow up visits the impedances values have been measured and stored for analysis. All the patients have been programmed with the best configuration and stimulation settings in terms of clinical outcomes.

Results: The mean value of the impedances, measured in 160 contacts in total (120 directional, 40 cylindrical) at baseline is 1976 Ohm for the directional contacts and 931 Ohm for the cylindrical ring contacts. In the following table and graph the mean and SD values of the impedance from baseline to up to 11 months follow-up are respectively for mean directional contacts (Ohm in 1st column) and for Mean ring contacts (Ohm in 2nd column): baseline (160 contacts):1976 (736,18 SD)  931 (281,66 SD)
1 month (144 contacts):2568 (662,49 SD)  1198 (240,81 SD)
6 months (112 contacts):2748 (676,21 SD)  1265 (258,06 SD)
11 months (48 contacts):3045 (618,92 SD)  1309 (191,70 SD)
Considering only the therapeutic contacts among the 7 patients who have reached the 6 month follow up, across a total of 40 contacts activated, 39 are directional.
Conclusions: The fluctuations of the impedances in the active directional contacts appear to be greater than in the standard cylindrical contacts. Moreover, high changes has been recorded also between adjacent active directional contacts. For these reasons the use of a Directional DBS system with independent power sources seems to be a proper tool to use constant-current stimulation to maintain the therapeutic stability when more than two contacts are activated in the same lead.

<table>
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<th>mean directional contacts (Ohm) (SD)</th>
<th>Mean ring contacts (Ohm) (SD)</th>
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<tr>
<td>baseline (160 contacts)</td>
<td>1976 (736,18)</td>
<td>931 (281,66)</td>
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<td>3045 (618,92)</td>
<td>1309 (191,70)</td>
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![Mean Impedances Graph]

<table>
<thead>
<tr>
<th>Therapeutic Contacts in 6 months after implant</th>
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<tr>
<td>Mean Impedance (Ohm)</td>
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<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>LEFT</td>
</tr>
<tr>
<td>PAT1 2403,72</td>
</tr>
<tr>
<td>PAT2 2332,33</td>
</tr>
<tr>
<td>PAT3 1991,78</td>
</tr>
<tr>
<td>PAT4 2454,11</td>
</tr>
<tr>
<td>PAT5 2372,00</td>
</tr>
<tr>
<td>PAT6 1289,50</td>
</tr>
<tr>
<td>PAT7 2757,44</td>
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</table>
Combined administration of the A2A receptor antagonist preladenant and the 5HT1A/1B receptor agonist eltoprazine prevents L-DOPA-induced dyskinesia in a rat model of Parkinson’s disease

Micaela Morelli, Giulia Costa, Nicola Simola, Manolo Carta, Marcello Serra, Annalisa Pinna

Department of Biomedical Sciences, University of Cagliari; National Research Council (CNR); Neuroscience Institute Cagliari, Italy

Objective: To evaluate whether an early co-administration of eltoprazine plus preladenant may prevent the onset of L-DOPA-induced dyskinesia and counteract the induction of the early gene zif-268.

Background: The serotonin 5-HT1A/1B receptor agonist eltoprazine suppressed L-DOPA-induced dyskinetic movements in animal models of Parkinson’s disease (PD) reducing, however, L-DOPA efficacy. In contrast, the adenosine A2A receptor antagonists preladenant increased L-DOPA efficacy without exacerbating dyskinetic-like behavior in animal models of PD.

Methods: Unilateral 6-OHDA-lesioned rats were treated for two weeks with eltoprazine (0.6 mg/Kg) and/or preladenant (0.3 mg/kg), alone or in combination with L-dopa (4 mg/kg) and abnormal involuntary movement (AIMs) as index of dyskinesia, were evaluated. Four days after the last drugs administration all rats were challenged with L-DOPA and AIMs and induction of the immediate-early gene zif-286 were evaluated as index of long-term changes correlated with dyskinesia.

Results: Results show that co-administration of L-DOPA plus eltoprazine and preladenant delayed the onset and produced a significant reduction of L-DOPA-induced dyskinesia. Moreover, results indicated that administration of L-DOPA, with or without preladenant, increased zif-268 levels in the caudate-putamen while L-DOPA plus eltoprazine, with or without preladenant, showed lower level of zif-268 activation after drugs treatment.

Conclusions: Results suggest that combination of L-DOPA plus preladenant and eltoprazine could be a promising pharmacological strategy to ameliorate L-DOPA efficacy and prevent the onset of L-DOPA-induced dyskinesia in PD.

Lack of Rhes protein increases dopamine neurons degeneration and neuroinflammation in a gender dependent manner

Micaela Morelli, Giulia Costa, A Usiello, Nicola Simola, F. Porceddu, L. Contu, F. Napolitano, Annalisa Pinna

Department of Biomedical Sciences, University of Cagliari. National Research Council (CNR), Neuroscience Institute, Ceinge Biotecnologie Avanzate, Naples, Italy

Cagliari, Italy

Objective: Considering the differential incidence of PD between the male and female population and the critical role of Rhes protein in survival of DA neurons, we have investigate neurotoxic and neuroinflammatory markers in Rhes−/− (KO), male and female mice, adult (3 months of age) and elderly (12 month of age).

Background: Rhes is a small GTP-binding protein highly expressed in the caudate-putamen (CPu), in neurons of substantia nigra pars compacta (SNC) and ventral tegmental area (VTA). Rhes knockout (KO) mice display an age-dependent reduction in TH-positive neurons in SNC as well as in motor speed, coordination and balance. Rhes, might therefore affect the vulnerability of dopaminergic (DA) neurons contributing to neuronal cell death triggered by aging, drugs or by neurodegenerative disease as Parkinson’s disease (PD).
Methods: Immunohistochemistry of tyrosine hydroxylase (TH)-positive neurons, microglial and astroglial activation by complement receptor type 3 (CD11b) and glial fibrillary acidic protein (GFAP) were performed in male and female mice Rhes knockout (KO) or wild type (WT).

Results: Adult Rhes KO male mice showed a significant decrease in density of DA neurons and fibers in the SNc and in CPu, as compared with male wild type (WT) and with KO female mice in the SNc. Adult KO female mice showed a decrease in TH in the SNc but not CPu as compared with WT mice. In contrast in elderly KO male and female it was observed a significant decrease in TH immunostaining both in CPu and SNc, as compared with WT mice. Adult Rhes KO male mice showed a significant increase in GFAP immunostaining in CPu, as compared with WT and in CPu and SNc, as compared with female mice. No modifications in GFAP immunostaining were observed in adult Rhes KO female mice, either in CPu or in SNc. Elderly Rhes KO male mice showed a significant increase in GFAP immunostaining in SNc but not in CPu, as compared with WT, whereas no modifications in GFAP immunostaining were observed in elderly Rhes KO female mice, either in CPu or in SNc. In addition adult Rhes KO male mice showed a significant increase in CD11b both in CPu and SNc, as compared with male WT and female KO mice. Elderly KO male mice showed a significant increase in CD11b immunostaining in SNc as compared with WT and in CPu as compared with female mice, whereas elderly KO female mice showed a significant increase in CD11b immunostaining in CPu, but not in SNc.

Conclusions: The more marked DA neuron degeneration and neuroinflammatory processes in male as compared to female Rhes KO mice, while confirm the role of Rhes as an important factor for DA neuron survival, gives support to the Rhes KO mice as a model for studying PD.

LBA 14
Concordance for Parkinson’s disease in twins: A 20-year update

Samuel Goldman, Ruth Ottman, Cheryl Meng, Kathleen Comyns, Kenneth Marek, Caroline Tanner

University of California-San Francisco, San Francisco Veterans Affairs Health System, Columbia University, Institute for Neurodegenerative Disorders
San Francisco, CA, USA; New York, NY, USA; New Haven, CT, USA

Objective: To update our prior estimates of concordance for PD in monozygotic (MZ) and dizygotic (DZ) twin pairs.

Background: Genetic contributions to disease traits can be estimated by comparing concordance rates in MZ (identical) and DZ (fraternal) twin pairs. During the 1990s, we conducted a cross-sectional study in 17,000 members of the NAS/NRC WWII Twins Cohort born between 1917-1927. We found high MZ:DZ concordance in pairs with PD diagnosed < age 50, but similar MZ:DZ concordance in those diagnosed > 50.[1] This is consistent with a genetic basis for young-onset disease, but a largely environmental basis for typical onset disease. However, because a large proportion of unaffected members of discordant pairs were still alive at last evaluation (mean age ~75), prior concordance estimates were based on incomplete data. ~95% of twins are now deceased.

Methods: We searched the National Death Index (NDI) for members of discordant twin pairs from our prior study, and obtained ICD codes for all underlying and contributing causes of death. PD was defined as PD diagnosed in our prior study, or ICD codes 332.0 or G20 listed on a death certificate. We updated previous estimates of concordance in MZ and DZ pairs, and calculated heritability and zygotity-specific risk and hazard ratios, both overall and in those with PD diagnosed age 50 in the first affected twin (twin-1).

Results: 13 twins (6 MZ, 7 DZ) were newly diagnosed with PD from NDI records. In total, we identified 235 pairs with PD in at least 1 twin, including 30 concordant (16 MZ, 14 DZ) and 190 discordant (78 MZ, 111 DZ, 1 unknown zygotity) pairs. 15 pairs were excluded due to unknown (8) or ambiguous diagnoses (7) in twin-2. Among concordant pairs, time from diagnosis in twin-1 until diagnosis in twin-2 averaged 9.1 years (median 7.0, range 1-31) in MZ and 10.6 years (median 8.0, range 1-36) in DZ pairs. In survival analyses, overall risk of PD in twin-2 was slightly higher in MZ than DZ pairs (hazard ratio 1.38, 95%CI 0.67-2.83). Heritability was ~0.7 in pairs with PD diagnosed 50.
Conclusions: Although concordance is slightly higher overall, these results confirm those of our prior study: genetic liability to PD is high in those with young onset disease, but low in those with typical age at onset. Relatively high concordance rates in DZ twins suggests possible effects of shared intrauterine or early childhood environment.

<table>
<thead>
<tr>
<th>PD Dx age in Twin-1</th>
<th>Zygosity</th>
<th>Concordant Pairs</th>
<th>Concordance</th>
<th>MZ:DZ Concordance Ratio (95% CI) &amp; Heritability (h²)</th>
<th>MZ:DZ Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>MZ</td>
<td>16/94</td>
<td>0.17</td>
<td>1.5 (0.8-3.0) H²= 0.13</td>
<td>1.38 (0.67-2.83)</td>
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<tr>
<td></td>
<td>DZ</td>
<td>14/125</td>
<td>0.11</td>
<td>1.6 (0.9-3.0) H²=0.15</td>
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<tr>
<td>≤ 50</td>
<td>MZ</td>
<td>4/6</td>
<td>0.67</td>
<td>3.3 (0.9-13.0) H²=0.51</td>
<td>3.76 (0.68-20.7)</td>
</tr>
<tr>
<td></td>
<td>DZ</td>
<td>2/10</td>
<td>0.20</td>
<td>3.75 (1.02-13.8) H²=0.73</td>
<td></td>
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<tr>
<td>&gt;50</td>
<td>MZ</td>
<td>12/85</td>
<td>0.14</td>
<td>1.4 (0.7-3.1) H²=0.11</td>
<td>1.28 (0.57-2.91)</td>
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<tr>
<td></td>
<td>DZ</td>
<td>11/112</td>
<td>0.10</td>
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LBA 15
Repetitive transcranial magnetic stimulation for treatment of limb-kinetic apraxia in Parkinson's disease

Jung E Park
Dongguk University Ilsan Hospital
Goyang, Korea

Objective: To report the effects of repetitive transcranial magnetic stimulation (rTMS) on limb-kinetic apraxia in Parkinson’s disease (PD).

Background: Apraxia, defined as inability to perform skilled or learned movements, is frequently seen in neurodegenerative diseases such as PD, corticobasal syndrome and Alzheimer’s disease. Apraxia is further classified into subtypes such as limb-kinetic, ideomotor or ideational apraxia. Although commonly overlooked and interpreted as impaired dexterity due to slowness, recent studies have shown that limb-kinetic apraxia does not correlate with bradykinesia in PD, suggesting that this is an independent phenomenon. Limb-kinetic apraxia, defined as the loss of the ability to make precise, independent and coordinated finger and hand movements, leads to impaired dexterity and has been shown to affect activities of daily living in Parkinson’s disease patients. To date, there is no effective treatment for limb-kinetic apraxia.

Methods: Eight PD patients underwent rTMS for treatment of limb-kinetic apraxia. All patients were clinically assessed via the Unified Parkinson Disease Rating Scale (UPDRS). Patients performed sequential unbuttoning and buttoning of a standardized gown they wore for assessment of limb-kinetic apraxia. The Apraxia Screen of TULIA (AST) was performed to evaluate for the presence of ideomotor apraxia. A 20-minute rTMS session of the left primary motor cortex (M1) was performed (10 Hz frequency, stimulation intensity of 80% resting motor threshold, 10 seconds/train and 20 trains) in the medication-ON state. Patients performed sequential unbuttoning and buttoning following rTMS both immediately and at 24 hours following the intervention.

Results: Eight PD patients underwent rTMS for treatment of limb-kinetic apraxia. All patients were clinically assessed via the Unified Parkinson Disease Rating Scale (UPDRS). Patients performed sequential unbuttoning and buttoning of a standardized gown they wore for assessment of limb-kinetic apraxia. The Apraxia Screen of TULIA (AST) was performed to evaluate for the presence of ideomotor apraxia. A 20-minute rTMS session of the left primary motor cortex (M1) was performed (10 Hz frequency, stimulation intensity of 80% resting motor threshold,
10 seconds/train and 20 trains) in the medication-ON state. Patients performed sequential unbuttoning and buttoning following rTMS both immediately and at 24 hours following the intervention.

Conclusions: Limb-kinetic apraxia in PD appears to improve with high-frequency rTMS of the left M1, as indicated by reduced time to perform sequential unbuttoning and buttoning, with delayed benefit at 24 hours. Noninvasive brain stimulation is being increasingly used for the treatment of various neurological disorders. Our results suggest that high-frequency rTMS may be effective in limb-kinetic apraxia, lending support to the need for future long-term studies to further determine if rTMS is truly efficacious in the treatment of this phenomenon.

LBA 16
Impact Of Intensive Courses In Engaging Young Neurologists Into Movement Disorders’ Subspecialty

Thiago Vale, Santiago Perez-Lloret, Margherita Fabbri, Tiago Teodoro; Tomás de la Riesta; Sèrgio A. Rodriguez-Quiroga; Joaquim J Ferreira; Wassilos Meissner; Charles H. Adler

1 Department of Internal Medicine, Federal University of Juiz de Fora, Juiz de Fora (MG), Brazil. 2 Institute of Cardiology Research, University of Buenos Aires, National Research Council (CONICET-ININCA), Buenos Aires, Argentina. 3 Clinical Pharmacology Unit, Instituto de Medicina Molecular, Faculty of Medicine, University of Lisbon, Portugal. 4 Institute of Cardiovascular and Cell Sciences, St George’s University of London, London, United Kingdom; Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal; Serviço de Neurologia, Hospital de Santa Maria, Lisboa, Portugal. 5 Coordinator of the Movement Disorders Clinic, INECO - Rosario, Argentina. 6 Neurogenetics Clinic and Movement Disorders Unit. University Center of Neurology and Department of Neurology. Jose Maria Ramos Mejia Hospital – Faculty of Medicine, University of Buenos Aires (UBA) Buenos Aires, Argentina. 7 Neurogenetics Unit, IRCCS Foundation Carlo Besta Neurological Institute, Via L. Temolo 4, 20126 Milan. Department of Medicine and Surgery, University Milan Bicocca, Via Cadore 48, 20900 Monza, Italy. 8 Instituto de Medicina Molecular, Faculty of Medicine, University of Lisbon, Portugal. CNS- Campus Neurológico Sénior, Torres Vedras, Portugal. 9 Service of Neurology, CHU de Bordeaux, Bordeaux, France; Université de Bordeaux, Institut des Maladies Neurodégénératives, UMR 5293, Bordeaux, France. 10 Professor of Neurology at Mayo Clinic College of Medicine; Mayo Clinic ; Phoenix, AZ, USA

Objective: Objective: To evaluate the participants’ perception of the impact of an intensive 2.5-day course combining lectures with practical training on movement disorders (MD), including examining patients, on their careers and on their choices to follow the MD subspecialty.

Background: Objective: To evaluate the participants’ perception of the impact of an intensive 2.5-day course combining lectures with practical training on movement disorders (MD), including examining patients, on their careers and on their choices to follow the MD subspecialty.

Methods: Methods: A web-based survey was performed. All participants from previous International Parkinson and Movement Disorders Society (MDS) Schools for Young Neurologists (2008-2014) were invited to participate in a web-based questionnaire.

Results: Results: A total of 283 out of 650 (43.5%) participants completed the survey. Almost 80% considered that the course had a direct impact on their involvement in the MD field. Of the 75 participants who had completed residency at the time of the survey, the number of those who are working as MD specialists increased from 34 (45.3%) at the time of the school to 72 (96%) at the time of the survey. Accordingly, the proportion with at least 25% of their weekly time spent practicing MD increased from 48.7% to 70% and MD was the main area of interest for 77.2%. Involvement in academic and teaching activities in MD increased from 48.6% up to 92.7%. Additionally, the percentage of MDS membership increased from 39.6% to 86.6%.

Conclusions: Conclusions: Young clinicians with a particular interest in MD reported a significant impact of attending a MDS School for Young Neurologists. Following completion of the schools, an increased number have become MD specialists and engaged in specialized academic and teaching activities in MD.
**Objective:** ALSP is caused by mutations in the colony-stimulating factor 1 receptor (CSF1R); it is a rare but devastating neurogenetic disorder that lacks causal treatment, thus leading to death within a few years. This is in part due to an incompletely understood disease etiology, but also due to the lack of a biomarker for early stages of the disease (asymptomatic mutation carriers) and for disease progression. This project aims to identify a monitoring marker for CSF1R mutation carriers and ALSP patients as a basis for the development and monitoring of treatment options.

**Background:** Neurofilament light chain (NfL) in blood and cerebrospinal fluid (CSF) was recently identified as potent biomarker for proteopathic neurodegenerative diseases (Bacioglu et al, Neuron, 2016). NfL is one of the scaffolding proteins of the neural cytoskeleton; following axonal damage, NfL levels in the serum and CSF increase and thus represent a biomarker for neuronal loss. Biomarkers are essential in clinical routine not only to monitor disease progression but also to evaluate treatment response. Rare neurogenetic disorders, however, often lack such markers. This impedes an early diagnosis and hinders research on treatment development.

**Methods:** NfL levels in serum and/or CSF were determined in 5 ALSP patients (aged 44.75 ± 8.015 (SD)), 2 asymptomatic CSF1R mutation carriers (aged 29 ± 4.242 (SD)) and 16 healthy controls (total controls: aged 47.375 ± 19.4 (SD); controls aged-matched to mutation carriers: 25.2 ± 7.823 (SD); controls age-matched to ALSP patients: 52.3 ± 7.58 (SD)). NfL concentrations were analyzed by a previously established electrochemiluminescence immunoassay (Gaiottino et al, PLoS One, 2013). Statistical significance was assessed using unpaired two-tailed t-test (assuming Gaussian distribution and equal standard deviations). Results are shown as mean ± standard error of the mean (SEM) in pg/ml (NfL) or years (age), unless otherwise specified (SD, standard deviation).

**Results:** 1) NfL levels in serum and CSF are age-dependent. Our results on NfL in serum and CSF confirm that in healthy controls, NfL increases with increasing age (Figure 1A and B, first panel). 2) NfL levels are increased in serum and CSF of CSF1R mutation carriers compared to age-matched controls. The NfL level in serum of mutation carriers was on average twice as high as in healthy controls (controls: 14.7 ± 2.294, n=5; mutations carriers: 28.9 ± 1.6, n=2; Figure 1A, middle panel). In CSF, NfL level in the mutation carrier was considerably higher (985.4, n=1) than in healthy controls (370.52 ± 159.524, n=5); however, there was one outlier among the healthy controls that had comparably high NfL levels as the mutation carrier (Figure 1B, middle panel). 3) NfL levels are severely increased in serum and CSF of ALSP patients compared to age-matched controls. The NfL level in serum of ALSP patients was on average ten fold increased compared to healthy controls (controls: 24.55 ± 2.837, n=6; ALSP: 246.1 ± 34.89, n=4; Figure 1A, third panel). The difference was even more dramatic in CSF, with a more than 20-fold increase in ALSP patients compared to age-matched healthy controls (controls: 891.5 ± 246.6, n=6; ALSP: 20041 ± 7228, n=5; Figure 1B, third panel).
Conclusions: Here we show that not only ALSP patients but also clinically asymptomatic CSF1R mutations carriers have increased NfL levels in serum and CSF compared to aged-matched healthy controls. Based on our results we will be able to detect early changes in asymptomatic CSF1R mutation carriers and evaluate the response to potential therapeutic compounds using NfL levels in serum and CSF. This provides the first step towards the development of a therapy for ALSP.

LBA 18
Interocular asymmetry of macular inner retinal layer thickness and disease severity in Parkinson’s disease: Optical coherence tomography study

Shahnaz Miri, Sofya Glazman, Eric M. Shrier, Yin Ding; Ivan Selesnick; Ahra Joh; Ivan Bodis-Wollner

Neurology Department, Medstar Georgetown University Hospital; Neurology and Ophthalmology Departments, SUNY Downstate Medical Center; SUNY Eye Institute; New York University, School of Engineering
Washington, DC, USA; Brooklyn, NY, USA

Objective: To perform interocular asymmetry (IOA) analysis of macular inner retinal layer (IRL) in Parkinson’s disease (PD) and to evaluate its correlation with disease duration and severity.

Background: Over the last decade, optical coherence tomography (OCT) of the retina has attracted much interest as a potential biomarker in PD, as an easily available, inexpensive, non-invasive device for the diagnosis and quantification of the disease progression.
Methods: In this retrospective study, macular OCT data of 92 patients with PD (184 eyes) was reviewed. Primary study variables were IRL thickness measures, disease severity (evaluated by UPDRS III and Hoehn and Yahr scores), and the disease duration. IRL thickness was compared between the two eyes of each subject in different distances from the foveola. Secondary study variables included age, ethnicity, gender. Statistical analysis was performed using SPSS 21.0 (Chicago, IL). P values P<0.05 were considered statistically significant.

Results: 92 patient were included (50 male and 47 female). The mean age was 66.4 ± 9.2, mean disease duration 4.8 ± 4.5 years, UPDRS III score 26.8 ± 6.5, and H&Y score 2.3± 0.4. There was a positive correlation between the disease duration and IOA at the foveola, inferior 0.25-0.5 mm, nasal 0.25-0.5mm, temporal 0.25mm, and superior 0.25mm distances from the foveola. UPDRS III and Hoehn and Yahr scores were also positively correlated with IOA at the same locations. The average central IOA (in a circular area with 0.5 mm diameter, centered at the foveola) was 2.42 ± 1.54 µ in stage 2, 5.79 ± 5.7µ in stage 3, and 9.80 ± 12.8µ in patients with stage 4. Age was not correlated with IOA.

Conclusions: In more advanced stages of PD, there is a significant IOA of central macular IRL thickness, suggestive of a potential marker for disease progression or monitoring.

LBA 19
Possible neuroprotective effect of quercetin against quinolinic acid induced neurotoxicity in rats: Behavioral, neurochemical and cellular evidences

Anil kumar, Jitendriya Mishra

Pharmacology Division, University Institute of Pharmaceutical Sciences, UGC-Centre of Advanced Study (UGC-CAS), Panjab University Chandigarh, India

Objective: The present study has been designed to investigate the neuroprotective potential of quercetin and its possible interaction with HDAC inhibitor against QA induced behavioral, neurochemical, cellular and histopathological alterations in rats.

Background: Huntington’s disease (HD) is an autosomal dominant progressive neurodegenerative disorder characterized by motor dysfunction (involuntary movements such as chorea and dystonia) followed by cognitive and psychiatric disturbances. Excitotoxic quinolinic acid (QA) striatal lesion model is widely known to mimic the pattern of HD pathology. Quercetin (3,3',4',5,7-pentahydroxyflavone), is a major dietary bioflavonoid, found particularly in citrus fruits, apples, onions, parsley, tea and red wine. Recently, potent antioxidant activities of quercetin in vitro have been exploited extensively to explore its neuroprotective potential in various experimental models.

Methods: QA (200 nmol) was administered bilaterally into the striatum to induce HD-like alteration in rats. Quercetin (20 and 40 mg/kg), valproic acid (100 mg/kg) were administered for 21 days. Various behavioral, biochemical,cellular and histopathological examination were made in discrete areas of the brain.

Results: Chronic treatment with quercetin (40 mg/kg) as well as valproic acid (100 mg/kg) for 21 days demonstrated significant amelioration of neurobehavioral deficits (motor & memory), oxidative damage (lipid peroxidation, nitrite concentration, super oxide dismutase and reduced glutathione), mitochondrial abnormalities (complex I, II, III and IV activities), cholinergic dysfunction (AchE activity), cellular alterations (TNF-α, caspase-3 & BDNF expression) aberrant neurotransmitter levels (adenosine & dopamine) as well as histopathological alterations following QA administration. However, quercetin at its lower dose (20 mg/kg) could not restore QA induced alterations, while its co-administration with valproic acid (100 mg/kg) showed marked neuroprotection.

Conclusions: Neuroprotective effect of quercetin is significantly potentiated in the presence of valproic acid against QA induced neurotoxicity in rats.
Objective: To create a standardized multidisciplinary model (MDM) of care which is cost effective, replicable and generic in order to overcome limited accessibility and acceptability of paramedical healthcare for PD in India.

Background: Parkinson’s disease (PD) affects multiple facets of one's life and its management demands a multidisciplinary approach to be adopted through pharmacological and paramedical therapies. In India, reliance on pharmacology is high and socio-cultural factors govern the use of paramedical therapy.

Methods: The MDM was developed, validated and applied over 3 phases. Phase I: Based on a needs analysis and in consultation with Movement Disorder Specialists, the need for the MDM to be educative and rehabilitative was inferred. The services of experts in Physiotherapy, Speech and Occupational Therapy, Psychology, Nutrition and alternative therapies were mobilized to author sessions. Scrutiny at several checkpoints led to modifications. Phase II: To evaluate its efficacy and establish it as a capacity training manual, a study was done by independent consultants with 15 people with Parkinson's (PwP) and 12 caregivers (CG) who were not previously exposed to paramedical therapies for PD. Qualitative and quantitative data was obtained on its effectiveness, concept, design, mode of delivery, relevance, acceptability, applicability.

Results: Paired t-test values between pre and post test data showed no significant differences on QoL, ADL and caregiver burden scores; however the mean values of each showed improvements in post–test scores in PwP and CG. Qualitative analysis revealed positive trends – perceived improved QoL and mobility, regained independence in ADL and skilled tasks, higher self-efficacy, improvement in emotional well–being and social support, and informed decision making. The MDM itself, was found to be clear and novel in content; easily deliverable by lay facilitators; comprehensible and relevant to PwP and CG; adaptable to different groups; time – effective; interest generating; logical in flow and sequencing of sessions; practical and beneficial; and effective in a group – format.

Conclusions: MDM was established as a capacity training manual and its current applications in India are:
• Education and rehabilitation of PwP and CG in 33 locations
• Replication of group rehabilitation centres in 19 locations based on local language translations
• Training of Parkinson’s care personnel in 11 cities and 1 Union Territories

Objective: (1) Apply micro-tissue engineering techniques to create living, implantable constructs that mimic the cytoarchitecture and function of the nigrostriatal pathway. (2) Validate the efficacy of these constructs when implanted en masse to physically reconstruct this pathway in a rat model of Parkinson’s disease (PD).

Background: The classic motor deficits of PD are caused by selective degeneration of dopaminergic neurons in the substantia nigra pars compacta, resulting in the loss their modulatory input to the striatum. Current treatments only
minimize the symptoms of this disconnection as, unfortunately, there is no approach capable of replacing the entire nigrostriatal pathway.

**Methods:** Constructs were created consisting of dopaminergic neurons with long unidirectional axonal tracts encased within hydrogel micro-columns designed to chaperone delivery into the brain. First, enriched populations of dopaminergic neurons were engineered into spheres using a forced cell aggregation method. Then, micro-columns were seeded with these dopaminergic neuronal aggregates, while lumen extracellular matrix (ECM), growth factors, and neuronal end targets were systematically varied to optimize cytoarchitecture and axonal extension. Finally, fully formed constructs were stereotaxically microinjected into rats with the perikaryal end placed in the substantia nigra and the axonal terminals deposited in the striatum.

**Results:** We found a 10-fold increase in axonal outgrowth from aggregates versus dissociated neurons, resulting in remarkable axonal lengths of >5mm by 14 days in vitro. Axonal extension was also dependent upon lumen ECM, but did not depend on growth factor enrichment or neuronal end target presence. Evoked dopamine release and synapse formation with striatal neurons was observed in vitro. Collectively, these techniques resulted in centimeter-scale neuronal-axonal constructs emulating the general structure and function of the nigrostriatal pathway by 1 month in vitro. Following microinjection in rats, construct neurons survived in the substantia nigra while maintaining their axonal projections to the striatum at 1 month post-transplant.

**Conclusions:** We have significantly advanced neural micro-tissue engineering techniques by creating transplantable constructs that mimic the general cytoarchitecture of the nigrostriatal pathway. This novel strategy may uniquely address gaps in current PD treatments by allowing simultaneous replacement of dopaminergic neurons in the substantia nigra as well as their long-distance axonal projections to the striatum.

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**LBA 22**
Abnormalities of age-related T-cell senescence characterise the immune profile in Parkinson’s disease

*Caroline Williams-Gray, Ruwani Wijeyekoon, Kirsten Scott, Joanne Jones, Roger Barker*

*Department of Clinical Neurosciences, University of Cambridge
Cambridge, United Kingdom*

**Objective:** It is critical to better understand the immune component of Parkinson’s disease (PD) given that this is such a tractable target for disease modifying therapy. This study aimed to address this need by determining the relevance of age-related changes in the adaptive immune system (immunosenescence) in this disorder.

**Background:** Our previous work indicates that the immune system contributes to PD, and has shown (i) genetic association between a key component of the adaptive immune response (HLA-DR) and PD risk, (ii) association between inflammatory cytokine profile and rate of disease progression, and (iii) delayed progression to PD dementia in individuals who regularly take non-steroidal anti-inflammatory drugs. Given that PD is more prevalent with increasing age, we have now investigated the relevance of age-related dysregulation of the immune system in this disorder, with a focus on T-cell replicative senescence, a key immune component of human ageing.

**Methods:** Peripheral blood mononuclear cells were extracted from blood samples collected from 40 patients with mild PD (Hoehn and Yahr stage 1-2, mean(SD) disease duration 4.3(1.2) years) and 40 age and gender matched controls. Immunophenotyping was performed with flow cytometry using markers of T-lymphocyte activation and senescence (CD3, CD4, CD8, HLA-DR, CD38, CD28, CCR7, CD45RA, CD57, CD31). CMV serology was measured given its proposed relevance in driving T-cell senescence.

**Results:** Markers of replicative senescence in the CD8 T-cell population were strikingly reduced in PD cases versus controls (reduced CD57 expression (p<0.005), reduced percentage of ‘late differentiated’ CD57low-CD28high cells (p=0.01) and ‘TEMRA’ cells (p=0.04)), whilst expression of activation markers (CD28) in the CD8 population was increased (p<0.005). This was not driven by any difference in CMV seropositivity between PD cases and controls. No significant changes were observed in the CD4 population.
Conclusions: This study demonstrates for the first time that the peripheral immune profile in PD is distinctly atypical for an older population, with a lack of the CD8 T-cell replicative senescence which characterizes normal ageing, and a shift towards more activated CD8 T-cells. The T-lymphocyte response warrants further investigation as a potential therapeutic target in PD.

LBA 23
Safety and Efficacy of DaxibotulinumtoxinA for Injection (RT002) in Isolated Cervical Dystonia: Results of a Phase 2, Dose Escalating Study

Cynthia Comella, Joseph Jankovic, Daniel Truong, Allison Brashear, Atul Patel, Marian Evatt, Carol Chung, Chad Oh, Roman Rubio
Rush University Medical Center, Neurological Sciences
Chicago, IL, USA

Objective: To report 24-week outcomes of an open-label trial of daxibotulinumtoxinA for injection (RT002) in isolated cervical dystonia (CD).

Background: Botulinum neurotoxins (BoNT) are considered first-line therapy for CD. The typical duration of beneficial effects is about 3 months. RT002 is a lyophilized product containing purified 150 kDa BoNT type A formulated with a novel excipient RTP004 that may reduce diffusive spread of BoNT to adjacent muscles and potentially extend treatment duration.

Methods: CD patients with Toronto Western Spasmodic Torticollis Scale (TWSTRS)-Total scores ≥20 and TWSTRS-Severity scores ≥15, who were BoNT naïve or had not received BoNT within the last 6 months, were enrolled in 3 consecutive RT002 dosing cohorts: up to 200 Units (U) of RT002 (n=12), 200-300 U of RT002 (n=12), and 300-450 U of RT002 (n=13). Safety data of each cohort were closely monitored prior to escalating RT002 dose to the next level. Primary efficacy endpoint was reduction in TWSTRS-Total score at Week 4. Subjects were evaluated at 2-4 week intervals for 24-36 weeks or until loss of benefit to assess safety and the duration of effect.

Results: As of 8 December 2016 (analysis for the primary endpoint), the study had completed 24 weeks for Cohort 1, 16 weeks for Cohort 2 and 4 weeks for Cohort 3. The mean age of 37 subjects was 56 years, 76% were females, and mean CD duration was 7.6 years. Mean baseline TWSTRS-Total and TWSTRS-Severity score was 44.1 and 21.1, respectively. At Week 4, a clinical meaningful mean reduction of 16.8 points (or 38%) in TWSTRS-Total Score was observed. The mean reduction at Week 4 was 7.1 points (or 34%) in TWSTRS-Severity score and 15.2 points (or 29%) in CD Impact Profile-58. Median duration of maintaining ≥20% of improvement achieved at Week 4 in TWSTRS-Total score was >24 weeks for Cohort 1. Treatment-related adverse events (AE’s) occurred in 35% of subjects, including mild, transient dysphagia (11%), injection site erythema (8%), and neck weakness (5%). The study is ongoing. As of 15 March 2017, all AE’s were mild to moderate, except for a case of severe neck pain that lasted for 2 days. No serious AE’s were reported.

Conclusions: The study shows that daxibotulinumtoxinA is generally safe and well tolerated, and may provide a long-lasting reduction in CD symptoms. Outcomes at 24+ weeks will be reported for all subjects.
Objective: To assess the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) effects of BMS-986168 on free extracellular tau (eTau) after intravenous (IV) infusions of BMS-986168 every 4 weeks (Q4W) in patients with progressive supranuclear palsy (PSP).

Background: BMS-986168 is a humanized monoclonal antibody that recognizes human eTau. In transgenic mouse models of tauopathy, the murine analog of BMS-986168 lowered free eTau concentrations in serum and cerebrospinal fluid (CSF) and limited the spread of tau pathology. In a previous phase I trial, single doses of BMS-986168 (up to 4200 mg) suppressed free eTau in the CSF of healthy subjects and were safe and well tolerated. Based on preclinical and phase I data, this exploratory study was designed to evaluate the safety profile of BMS-986168 and its ability to reduce free eTau in the CSF of patients with PSP.

Methods: This was a randomized, double-blind, placebo-controlled, multiple ascending dose trial of 48 patients with PSP, of whom 12 (25%) received placebo. Three ascending dose panels (150 mg, 700 mg, and 2100 mg) comprised of 8 patients per panel, were administered IV infusions of BMS-986168 (6 patients) or placebo (2 patients) Q4W for 12 weeks; an additional 24 patients were treated with BMS-986168 at a dose of 2100 mg (18 patients) or placebo (6 patients) administered Q4W for 12 weeks. All patients were also offered the opportunity to participate in an open-label extension study. Safety assessments and serum and CSF samples were collected over the 12 weeks. PK parameters (in serum and CSF), PD measures (concentrations of CSF free eTau), and corresponding change and percent change from baseline were evaluated. Clinical outcome measures including the PSP Rating Scale and Schwab and England Activities of Daily Living Scale were also employed.

Results: Patients’ mean age was 67.4 ± 5.5 years; 54.2% were female. Concentrations of BMS-986168 in serum and CSF increased with dose. The percentages of patients experiencing adverse events (AEs) were similar in the BMS-986168 and placebo groups (~75%). Most AEs were mild. There were no deaths or discontinuations due to AEs. Mean suppression of CSF free eTau was approximately 90–96% (Day 29) and 91–97% (Day 85) at doses ranging from 150 mg to 2100 mg. Although CSF and serum exposures and reductions of CSF free eTau increased with BMS-986168 dosage, significant reductions of CSF free eTau were observed with all dosages employed in the study.

Conclusions: Administration of multiple doses of BMS-986168 was safe and well tolerated at doses up to 2100 mg in patients with PSP. The robust suppression of CSF free eTau concentrations that was observed in this study further supports the potential utility of BMS-986168 in the treatment of human tauopathies. A phase II efficacy study in patients with PSP is ongoing (NCT03068468).
Motor fluctuations and levodopa-induced dyskinesias in an incident population-based Parkinson’s disease cohort: 13-year follow-up of the CamPalIGN study

Han-Joon Kim, Sarah Mason, Thomas Foltynie, Roger Barker, Caroline Williams-Gray

Department of Neurology and Movement Disorder Center, College of Medicine, Seoul National University, Seoul, Korea; John van Geest Centre for Brain Repair, Department of Clinical Neurosciences, University of Cambridge, Cambridge, United Kingdom; Sobell Department of Motor Neuroscience, Institute of Neurology, University College London, London, United Kingdom

Objective: To describe the development of motor fluctuations (MF) and levodopa-induced dyskinesias (LID) and their clinical and genetic risk factors in an incident population-based Parkinson’s disease (PD) cohort.

Background: The natural history of MF and LID in PD are still incompletely understood. Current knowledge is mostly derived from cross-sectional studies or clinical trials on selected patients, necessitating the need for a study on unselected patients followed from the point of diagnosis over a long follow-up duration.

Methods: The CamPalIGN cohort (Cambridgeshire Parkinson’s Incidence from GP to Neurologist) comprises incident cases of parkinsonism diagnosed between 2000 and 2002 within the county of Cambridgeshire, UK. One hundred forty-one patients with PD (79 men and 62 women) have been followed prospectively for up to 13 years. Clinical and neuropsychological testing were performed and presence or absence of MF and LID was evaluated at each follow-up visit. Genotyping was performed for candidate genes with potential prognostic significance including MAPT H1 versus H2 haplotype, SNCA rs356219, APOE ε-2/3/4 alleles, COMT Val158Met, BDNF Val66Met, and GBA wild type versus polymorphism or mutation. Kaplan-Meyer survival and Cox regression analyses were used to assess the cumulative incidence and baseline risk factors for MF and LID.

Results: Age at diagnosis was 70.2 ± 3.5 years. Over a mean follow-up duration of 7.8 ± 3.5 years, 83 patients (58.9%) developed MF and 39 (27.7%) developed LID. The 5-year cumulative incidence of MF and LID were 54.3% and 14.5%, respectively, and the 10-year cumulative incidence of MF and LID were 100% and 55.7%, respectively. In multivariate Cox regression analysis, higher total UPDRS score at baseline (p=0.004, HR 1.024) was independently associated with the increased risk of MF. Higher MMSE score at baseline (p=0.002, HR 1.509) and carrying a GBA SNP or mutation (as compared with carrying wild-type GBA) (p=0.009, HR 4.497) were independently associated with the increased risk of LID.

Conclusions: Virtually all patients experience MF at 10 years while only 56% have LID. Only disease severity at baseline (total UPDRS) independently predicted speed of development of MF. Preserved cognition (higher MMSE) and GBA genotype were associated with the risk of LID, but not markers of motor severity or equivalent levodopa dose. Preserved baseline cognition and GBA genotype may be markers of a more dopa-responsive disease phenotype which is prone to development of LIDs.

Cardiovagal and Cardiovascular adrenergic dysfunction in Drug-naive Parkinson's Disease; Correlation of Motor and Non-motor Symptoms

Heejeong Jeong

Department of Neurology, Gyeongsang National University Changwon Hospital
Changwon, Korea

Objective: To evaluate autonomic dysfunction in drug-naive PD and see the correlation with motor and non-motor symptoms.

Background: Non-motor symptoms, including autonomic dysfunction are frequently seen in early stage of idiopathic Parkinson's disease (IPD), usually disclose earlier than motor symptoms. To improve patient’s quality of
life, it is important to evaluate and manage nonmotor symptoms. In this study, we investigated autonomic
dysfunction using autonomic function tests (AFTs) in drug-naive IPD patients, assessed correlations with motor and
non-motor symptoms.

Methods: From July 2013 to March 2017, a series of 23 patients with drug-naive IPD and 51 healthy controls (HC)
underwent AFTs; heart rate difference to deep breathing, Valsalva maneuver, quantitative sudomotor axon-reflex
test and head-up tilt test. Also, Drug-naive IPD patients completed the Non-Motor Symptom assessment scale
(NMSS).

Results: Two of the 23 IPD patient showed orthostatic hypotension. Values for Heart rate difference during deep
breathing (HRdb), E:I ratio (Expiration:Inspiration ratio), Valsalva ratio (VR), baroreflex sensitivity (BRS)-a, BRS-
a1, BRS-v, pressure recovery time (PRT) and distal leg sweat volume were significantly impaired in drug-naive PD
compared to HC. HRdb correlated with NMSS-cardiovascular domain (r=-0.631, p<0.05) and NMSS-
attention/memory domain (r=-0.700, p<0.05). E:I ratio correlated with NMSS-cardiovascular domain (r=-0.631,
p<0.05). PRT significantly correlated with NMSS-urinary domain (r=0.654, p<0.05). NMSS-gastrointestinal domain
were correlated with sweat volume of proximal leg(r=-0.856, p<0.05), sweat volume of distal leg(r=-0.778, p<0.05)
and sweat volume of foot (r=-0.858, p<0.05). None of the AFTs parameters showed significant correlation with
motor symptoms (UPDRS, H&Y score).

Conclusions: Our investigation suggests that cardiovagal, cardiovascular adrenergic, postganglionic sudomotor
impairments are clearly seen in early stage, drug-naive PD. Also, non-motor symptoms (orthostatic intolerance,
attention/memory, urinary dysfunction) correlates with cardiovagal and cardiovascular adrenergic dysfunction.
Since sudomotor function showed no significant difference between Drug-naive PD and healthy control, correlation
of sudomotor function and gastrointestinal domain should interpretate with care. In conclusion, clinical AFTs can be
reliable objective tool to monitor non-motor symptoms in early stage of IPD.

Biomarkers in LRRK2 associated Parkinson’s disease

Esther Sammler, Ying Fan, Pavel Lis, Andy Howden, Kathrin Brockmann, Thomas Gasser, Dario Alessi

University of Dundee, MRC Protein Phosphorylation and Ubiquitylation Unit
Dundee, United Kingdom

Objective: To establish and validate an assay to robustly monitor LRRK2 mediated phosphorylation of endogenous
Rab proteins in human peripheral blood samples derived from control and PD patients with and without LRRK2
mutations.

Background: Parkinson’s disease (PD) is a life changing neurodegenerative condition that affects 1 in 100 people
over the age of 60. The pathogenesis of PD is complex and multifactorial. Genome-wide association studies
(GWAS) have identified at least 26 independent loci that increase the risk for developing the condition. Genetic
changes in the leucine-rich repeat kinase-2 (LRRK2) are the greatest known genetic contributor to Parkinson’s,
accounting for 1-2% of all cases and even more so (up to 40%) in people with certain ethnic background. Recent
work has revealed that LRRK2 directly phosphorylates a conserved Thr/Ser residue in the effector-binding switch-II
motif of a number or Rab proteins, including Rab7L1, Rab8A, Rab10 and Rab12. There is considerable interest in
exploring whether LRRK2 kinase inhibitors may have therapeutic benefit for the treatment of PD.

Methods: We have developed an assay to quantitatively assess LRRK2-mediated phosphorylation of Rab proteins
and downstream effectors in biosamples derived from human peripheral blood cells. For this, 20ml of peripheral
blood was drawn from healthy volunteers for granulocyte isolation by negative selection. Purity of the isolation step
was checked by flow cytometry. Cells were then treated with the specific LRRK2 kinase inhibitor MLi-2 and
DMSO (dimethyl sulfoxide) as a negative control before cells were lysed. The phosphorylation status of LRRK2
autophosphorylation sites and LRRK2 mediated phosphorylation of Rab10 was assessed by phos-tag as well
Western blotting with phospho-specific antibodies. In a next step, we tested he effect of delayed sample processing
after blood collection as this important for implementing our assay in clinical practise. Furthermore we have pilot data from patients with and without LRRK2 associated PD and controls. Ethical approval for our study is in place.

**Results:** See figure: We show that endogenous LRRK2 can be detected in human peripheral blood cell lysates from healthy volunteers by Western blotting and that the LRRK2 inhibitor MLi-2 induces complete dephosphorylation of the endogenous LRRK2 Serine 935 autophosphorylation site. Purity of our granulocyte cell population is high (>96.9%). We then show that Rab 10 is de-phosphorylated in the presence of the LRRK2 kinase inhibitor MLi-2. Furthermore, delayed processing of up to 24 hours after blood collection has no negative effect on the assay. Pilot data from patients and controls suggests that LRRK2 mediated Rab phosphorylation is slightly increased in the disease groups.

**Conclusions:** The 2 main implications of our study to assess the LRRK2 mediated phosphorylation of Rab proteins in human blood samples in vivo are: Firstly, several pharmaceutical companies are undertaking pre-clinical research with promising LRRK2 inhibitors. Developing robust assays to detect the impact of LRRK2 inhibitors on Rab phosphorylation in samples derived from peripheral blood would be greatly advantageous for future clinical trials. Such assays could be used to assess efficacy and target engagement of administered LRRK2 inhibitors. Secondly, better assays to assess LRRK2 mediated phosphorylation could be exploited to monitor LRRK2 pathway activity in PD patients.

![Image of LRRK2 mediated phosphorylation of Rab10 in human neutrophils in vivo](image)

(A) Purity and Efficacy of Neutrophil Isolation from 20ml of Human Peripheral Blood.

(B) Human peripheral blood neutrophils from 12 healthy volunteers were treated with 0.1% (v/v) DMSO (-) and 10mM MLi-2 (+) in either RPMI media or PBS for 30 minutes. Cell lysates were prepared and immunoblotted for non-phosphorylated LRRK2 using 2 different LRRK2 antibodies. MLi induced complete dephosphorylation of the endogenous LRRK2 Ser935 autophosphorylation site. This is demonstrated by using phospho-specific antibodies for the pSerine935.
(C) LRRK2 mediated phosphorylation of endogenous Rab10, in the absence or presence of the specific LRRK2 inhibitor MLi-2 was analyzed by Phos-tag assay using an anti-total Rab 10 antibody. Bands corresponding to phosphorylated and non-phosphorylated Rab10 are marked with open (○) and closed (●) circles respectively. LRRK2 dependent Rab10 phosphorylation is detected in all donors.

LRRK2 mediated phosphorylation of Rab10 in human neutrophils in vivo

(D) Delayed processing experiments: Feasibility study for future study in patient samples – LRRK2 control blots

(E) Affinity purified rabbit polyclonal p-Rab8 antibody readily detects Rab8/Rab10 phosphorylation in human neutrophils, evidence that blood can be stored at room temperature from 24 hours prior to neutrophil isolation without impacting on LRRK2-mediated Rab phosphorylation. Lior analysis will be performed from now on to enable improved quantification of data.
LBA 28
SIAXI: Efficacy and safety of incobotulinumtoxinA for the treatment of sialorrhea in Parkinson’s disease (PD) and other neurological conditions: Results of a Phase III, placebo-controlled, randomized, double-blind study

Andrew Blitzer, Andrzej Friedman, Olaf Michel, Birgit Flatau-Baquè; János Csink; Wolfgang Jost

Department of Otolaryngology-Head and Neck Surgery, Columbia University College of Physicians and Surgeons; Department of Neurology, Icahn School of Medicine at Mt. Sinai, NYC; Department of Neurology Faculty of Health Science Medical University of Warsaw, Poland; Otorhinolaryngology University Hospital Brussels, Belgium; Merz Pharmaceuticals, Frankfurt Germany; Parkinson-Klinik Wolfach, Germany

New York, NY, USA

Objective: We report on the largest controlled study to date of incobotulinumtoxinA (Xeomin®) in the treatment of sialorrhea due to PD and other etiologies.

Background: Sialorrhea (drooling) can be a troublesome and disabling symptom resulting from various causes including Parkinson’s disease (PD), cerebral palsy, amyotrophic lateral sclerosis (ALS) and various degenerative brain disorders. The most devastating consequences of it are aspiration pneumonia, perioral skin breakdown, embarrassment, social isolation and economic impact in care.

Methods: Eligible subjects were adults with chronic, troublesome sialorrhea due to PD, atypical Parkinson syndromes, stroke, or traumatic brain injury. Subjects were randomly assigned in a double-blind fashion to receive either 75U or 100U incobotulinumtoxinA or placebo. Dosing and injection sites were: 15U or 20U into each submandibular gland; 22.5U or 30U into each parotid gland in the lower dose group and higher dose group, respectively. Subjects were followed for 16±2 weeks after injection. Co-primary outcomes were: Unstimulated Salivary Flow Rate (uSFR) at week 4 compared to baseline and Global Impression of Change Scale (GICS) at Week 4 post-injection. Multiple secondary outcomes as well as other efficacy measures (Drooling Severity and Frequency Scale - DSFS, modified Radboud Oral Motor Inventory in Parkinson’s Disease - mROMP drooling) and safety data were also collected.

Results: A total of 184 subjects received either 75U (n=74); 100U (n=74); or placebo (n=36). Sialorrhea etiologies by percentage were: PD 70.6%, atypical Parkinson syndromes 8.7%, stroke 17.9%, traumatic brain injury 2.7%. Injection sites were localized by anatomical landmarks in 43.5% and ultrasound (US) guidance in 56.5%. The 100U incobotulinumtoxinA group showed -0.13 g/min (SE 0.026, 95%CI) LS-mean uSFR reduction and +1.25 (SE 0.144,
95%CI) score points LS-mean improvement on GICS at week 4 compared to baseline pre-injection. Both co-primary outcomes demonstrated statistically significant results in the 100U dose group vs. placebo (uSFR - 0.04g/min, SE 0.21; GICS +0.67, SE 0.186) at week 4 (p<0.005). The 75U dose was more effective than placebo, however without statistically significant difference at week 4. Secondary analyses revealed significant improvement in both uSFR and GICS at week 8 and 12 post-injection in both active treatment groups with maintained improvement in the uSFR in both dose groups at the last observation point at week 16. Further measures of efficacy (DSFS and mROMP drooling) confirmed the effectiveness of both active groups providing robust and consistent data for a clinically relevant improvement. The study also confirmed the favorable safety and tolerability profile of incobotulinumtoxinA in this indication; no new or unexpected safety signals were identified.

**Conclusions:** Injection of doses of 75U and 100U of incobotulinumtoxinA (Xeomin) into the submandibular and parotid salivary glands, with a dose distribution of 3:2, are effective up to 16 weeks for treatment of troublesome chronic sialorrhea in PD and in other neurological conditions with more beneficial results for the 100 U treatment without meaningful added risks for adverse effects.

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**LBA 29**

First results from a prospective double blind crossover trial comparing DBS of the posterior subthalamic area to thalamic DBS in ET patients

*Michael T. Barbe, Paul Reker, Stefanie Hamacher, Jeremy Franklin, Daria Kraus, Till A. Dembek, Johannes Becker, Julia Steffen, Niels Allert, Jochen Wirths, Jürgen Voges, Gereon R. Fink, Veerle Visser-Vandewalle, Lars Timmermann*

*University Hospital Cologne*
*Cologne, Germany*

**Objective:** To investigate deep brain stimulation (DBS) of the posterior subthalamic area (PSA) in a prospective study and to compare PSA and thalamic (VIM) DBS in a double-blind cross-over setting in patients with essential tremor (ET).

**Background:** While the VIM has been the target of choice for DBS in ET for a long time, several case series, cross-sectional observations, retrospective studies, and one prospective study suggested that PSA might be an equally or even more effective target. No prospective studies comparing PSA-DBS to VIM-DBS exist so far.

**Methods:** Fourteen ET-patients eligible for DBS completed a prospective double-blind crossover study (for a detailed study protocol see Barbe et al., Trials, 2016). DBS leads were bilaterally implanted with at least one electrode contact per hemisphere positioned inside the PSA, one at the ventral border of the thalamus (“neutral”) and one inside the VIM. Three months after implantation patients were randomized to either two months of PSA-DBS followed by two months of VIM-DBS or vice versa. The primary research question was tremor reduction according to the tremor rating scale (TRS) at the end of the PSA-DBS period compared to preoperative baseline. The secondary research question was the comparison between PSA- and VIM-DBS. In addition to tremor, quality of life, ataxia and gait, number and intensity of adverse events and stimulation amplitudes were analyzed. The data was fully monitored.

**Results:** PSA-DBS led to a highly significant reduction in the TRS total score of about 64 % compared to baseline. When comparing PSA-DBS to VIM-DBS, there were statistical trends towards higher tremor suppression as well as less subjectively perceived speech impairment during PSA-DBS. Stimulation amplitudes for tremor control were significantly lower during PSA-DBS.

**Conclusions:** Our results demonstrate that the PSA is a very effective surgical target in the treatment of ET. Tremor suppression in the PSA is at least equally or even slightly more effective than in the VIM and can be achieved at significantly lower stimulation amplitudes.
Objective: A pilot study to characterize Emergency Department (ED) utilization and referral patterns in undiagnosed Parkinson’s Disease (PD) patients.

Background: Prior ED encounters following the diagnosis of PD predict higher rates of future encounters (1). Surprisingly, virtually nothing is known about ED utilization in not-yet diagnosed PD patients. With more than 125 million ED visits each year in the U.S., an unrecognized opportunity exists to identify and refer potentially undiagnosed patients earlier in the course of the disease, facilitating better outcomes and entry into clinical trials. Unlike seizure and stroke, there is a woeful lack of collaboration between the fields of Emergency Medicine (EM) and the Movement Disorder specialties when it comes to the goal of early identification of patients with these conditions.

Methods: In preliminary research we have already identified 7976 individuals (living and deceased) within the Kaiser NorCal patient database. Of 7976 patients with Parkinson’s diagnosis within the Kaiser system, 5889 (~74%) had ED visits in the 2 years preceding the diagnosis. We then manually reviewed 15 charts in order of appearance in our series and examined them for ED visits during periods of 5 and 2 years prior to diagnosis and 2 and 5 years after diagnosis, respectively. A literature search followed by manual review of all candidate articles was undertaken to understand the scope of EM presence in the PD literature for the purpose of assessing overlap between the fields of EM and PD.

Results: Of 7976 PD patients within the Kaiser NorCal 5889 (73.8%) had ED visits in the 2 years preceding the diagnosis 14 of 15 (93%) of reviewed charts correctly identified patients with the diagnosis made or confirmed by a neurologist while one patient was excluded for having entered the Kaiser system with an existing diagnosis. The average number of ED visits prior to diagnosis compared to ED utilization following diagnosis (Figure 1): 0 to 5 years prior to diagnosis: Avg 4.8 ED visits (95% CI: 2.8 to 6.8). 0 to 5 years after diagnosis: Avg. 2.7 ED visits (95% CI 1.0 to 4.5). During the 2 year window preceding the diagnosis: Avg 3.1 (95% CI 1.7 to 4.5). 2 years following diagnosis: Avg. 1.3 (95% CI 0.3 to 2.3). The most commonly PD associated signs and symptoms identified by Emergency physicians prior to diagnosis, by rank order: Syncope/Near Syncope/Orthostatic Hypotension > Falls > Monarticular orthopedic complaint > Gait abnormality > Tremor > Anxiety/Depression > Voice change/Swallowing difficulty. Between 1923 and the last day of 2016 there are 64,218 PubMed references mentioning PD while only 176 even contain the word “emergency” in title or abstract and only 58 were specifically related to the ED as research, review or case report. Of these 58 only 10 had identifiable Emergency Medicine authors (0.1% and 0.015% of PD referencing literature, respectively). No article in the 93 year period appears to characterize ED utilization and referral patterns prior to the diagnosis of PD (Figure 2).
Conclusions: Autonomic instability and falls are highly common presentations of undiagnosed PD while tremor seems less uncommon perhaps because the sign is more familiar to patients and their physicians so the diagnosis is more often suspected. ED utilization was significantly higher prior to diagnosis than after diagnosis of PD. With more than 60 million of 125 million annual ED visits each year by patients over the age of 50--many with signs and symptoms such as fall injuries, syncope, pain and prodromal symptoms such as constipation the opportunity to flag and refer a potential movement disorder remains neglected by EM and Neurological services encountering ED patients. Until there is coordinated research and strategy development, the goals of reducing ED referral, early diagnosis and chronic under-enrollment by PD clinical trial investigators will remains unrealized. Our results and demonstration of the general absence of movement disorder research in EM literature is evidence of this unmet patient need and opportunity to advance research in a heretofore unrecognized, but likely important clinical arena.
LBA 31
MRI-guided laser interstitial thermal thalamotomy for medically intractable tremor disorders

Meghan Harris, John Steele, Richard Zweig, Jessica Wilden
Willis-Knighton Health System
Shreveport, LA, USA

Objective: To describe five cases of medically intractable tremor treated with unilateral laser interstitial thermal therapy (LITT) thalamotomy performed under real-time MRI guidance.

Background: Medically intractable tremors are a common and difficult clinical situation. DBS decreases tremors, but not all patients are candidates socially or medically. Thalamotomy has been accomplished with multiple modalities, all of which fail to deliver on key aspects of patient satisfaction. Specifically, radiofrequency and ultrasound require intra-procedural testing, ultrasound requires shaving the entire head, and radiosurgery requires frame placement coupled with a delay to achieve tremor control. As the population ages and economic concerns mount, there is increasing demand for a tremor procedure that meets the following criteria: 1. No hardware, 2. No titration, 3. Fast results, 4. No patient participation in procedure, 5. Minimal incision, and 6. Minimal recovery.

Methods: Five appropriate patients since January of 2017 were identified for the novel thalamotomy procedure. Reasons for thalamotomy over DBS included: 1. Advanced age, 2. Social factors, and 3. Medical co-morbidities. All patients strongly preferred general anesthesia even with the stated risk of uncertain tremor/side effects. Each patient underwent a unilateral LITT thalamotomy using Visualase therapy under live MRI guidance in combination with the Clearpoint stereotactic system. Six critical safety points were set around the planned ablation, four arranged circumferentially around the axial target (1A) and one at the capsular border (2B). This treatment resulted in a ~6 mm spherical ablation of the VIM thalamus on post-contrast T1-weighted MRI (1C).

Results: All patients had an acute decrease in tremor immediately post-operatively, which has been sustained through the short-term. Incisions were minimal. The decrease in hand tremor has resulted in improved daily function, including hygiene, eating, drinking, and writing in all patients. No patient had a permanent, disabling side effect of thalamotomy. One patient had mild transient left-sided weakness that was not functionally disruptive and resolved over a few weeks with steroids.

Conclusions: Long-term outcomes for this procedure have yet to be established. Limitations notwithstanding, LITT thalamotomy may be a useful alternative to other methods for medically intractable tremor disorders.
Increased Error Rate on the Antisaccade Task: a Sign of Prefrontal Involvement in Idiopathic REM Sleep Behavior Disorder.

Jaromír Hanuška, Jan Rusz, Olga Ulmanová, Cecilia Bonnet, Petr Dušek, Veronika Ibarburu, Tomáš Nikolai, Ondřej Bezdiček, Karel Šonka and Evžen Růžička

a) Dept. of Neurology and Centre of Clinical Neuroscience, Charles University, 1st Faculty of Medicine and General University Hospital, Prague, Czech Republic; b) Dept. Of Neurosurgery, Na Homolce Hospital, Prague, Czech Republic; c) Dept. of Circuit Theory, Faculty of Electrical Engineering, Czech Technical University, Prague, Czech Republic; d) AP HP, Neurology Department, Pitié Salpêtrière Hospital, Paris, France

Objective: The present study aims to characterize eye movement abnormalities in idiopathic REM sleep behavior disorder (iRBD) using infrared video-oculography (VOG).

Background: iRBD is a common prodromal non-motor symptom of Parkinson’s disease (PD) and other synucleinopathies. Although patients with PD present saccade abnormalities, it is unclear if they occur in the prodromal period. By assessing both saccades and antisaccades in subjects with iRBD and in de-novo PD, we aimed to see if they evinced abnormalities that may be associated with basal ganglia or frontal lobe dysfunction.

Methods: Fifty iRBD patients (45 males, mean age 66.4, SD 7.5 years), with polysomnography-confirmed RBD, 25 newly diagnosed, untreated PD patients (18 males, 62.8, 9.6), and 25 healthy subjects (20 males, 66.5, 9.0) were prospectively enrolled. VOG was investigated using both horizontal and vertical prosaccade and antisaccade paradigms. Clinical assessment included MDS-UPDRS and the Montreal Cognitive Assessment (MoCA) test.

Results: When compared to healthy controls, both iRBD and de-novo PD patients showed increased error rates in the horizontal antisaccade task (p < 0.05, p < 0.001, respectively) (Fig. 1). In addition, de-novo PD patients showed both hypometric horizontal prosaccades (p < 0.001) and prolonged latency in vertical prosaccades (p < 0.05) compared to controls. There was a deteriorating trend in iRBD, which parallels the significant changes observed in PD patients compared to controls (Fig. 2). MDS-UPDRS part III correlated to error rates in the horizontal antisaccade task (r =0.45, p < 0.01) only in the PD group. No correlations between MoCA and eye movement metrics were observed.
Conclusions: This is the first study to demonstrate abnormalities in saccadic eye movements in iRBD patients. Increased error rate in the antisaccade task reflects decreased ability to suppress a reflexive saccade that is attributed to the dorsolateral prefrontal cortex and may be related to mild impairments of executive functions and attention that have been reported in both iRBD and initial PD.
**LBA 33**

**Apomorphine formulation influences subcutaneous complications in continuous apomorphine pump therapy for Parkinson’s disease**

Peter Hagell, Arja Höglund, Carina Hellqvist, Eva-Lena Johansson; Berit Löved; Ann-Christine Sjöström; Carina Karlberg; Margareth Landgren; Nil Dizdar; Anders Johansson; Thomas Willows; Johan Rådberg; Filip Bergquist

The PRO-CARE group, School of Health and Society, Kristianstad University, Kristianstad, Sweden; Department of Neurology, Karolinska University Hospital, Stockholm, Sweden; Department of Neurology, University Hospital, Linköping, Sweden; Department of Neurology, Karlstad Central Hospital, Karlstad, Sweden; Department of Neurology, Sahlgrenska University Hospital, Gothenburg, Sweden

**Objective:** To explore if the occurrence and severity of subcutaneous (sc) nodules is influenced by the pharmaceutical formulation of apomorphine used for sc infusion in advanced Parkinson’s disease (PD).

**Background:** Apomorphine infusion is an effective therapy in advanced PD, but a limitation is troublesome sc nodules. Various chemically non-identical apomorphine formulations are available. Anecdotal clinical experience has suggested that shifting from one of these (Apo-Go PumpFill; apoGPF) to another (Apomorphine PharmSwed; apoPS, developed in Sweden) may influence the occurrence and severity of sc nodules.

**Methods:** In this multicenter open-label prospective observational study, 15 people with advanced PD (mean PD-duration, 13.4 years; median Hoehn & Yahr, IV) on apoGPF since a mean of 2.1 years and with troublesome sc nodules were switched to apoPS. Ongoing interventions to treat existing nodules (ultrasound, massage, Hirudoid cream) continued, and apomorphine as well as other drugs was managed according to clinical routines. Data were collected between May 2015 and March 2017; at baseline, at the time of switching (about 2 weeks later), and up to 1.7-4.2 (mean, 2.5) months post-switch follow-up. Primary outcomes were total nodule numbers, size (mm diameter for the 5 worst nodules), consistency (scored 0-3 for the 5 worst nodules), and associated skin changes (scored 0-4 for the 5 worst nodules) and pain (scored 0-5). Patients also rated their perceived PD severity and motor complications (UPDRS IV). Patient preferences 5-12 months post-switch (2-9 months after follow-up) were also recorded.

**Results:** Apomorphine and L-dopa doses did not change over the observation period (P≥0.400). Baseline nodule numbers (7.4 vs. 4.6; P<0.003), size (92.9 vs. 54.1 mm; P=0.016), consistency (11 vs. 5; P=0.003), skin changes (3 vs. 1.5; P=0.205), and average pain (1 vs. 0; P=0.020) improved 11 weeks post-switch. Patient-reported PD severity (P=0.020) and motor fluctuations improved (P=0.051), whereas dyskinesias tended to increase (P=0.205). At 5-12 months post-switch, 13 patients had decided to remain on apoPS; mainly due to improved nodules.

**Conclusions:** These observations suggest that apoPS may have a better safety profile compared to apoGPF in terms of sc nodule occurrence and severity. There is a need for larger, randomized controlled studies for firmer conclusions.

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**LBA 34**

**Inhaled levodopa (CVT-301, 84-mg dose) significantly improves motor function during OFF periods in Parkinson’s disease (PD) subjects: A phase 3 study [SPAN-PD]**

Peter A. LeWitt, Hubert H. Fernandez, Robert A. Hauser, Stuart H. Isaacson, Mark Lew, Rajesh Pahwa, Marie Saint-Hilaire, Cheryl Waters, Alexander Sedkov, Richard Batycky, Charles Oh

Henry Ford Hospital and Wayne State University School of Medicine
West Bloomfield, MI, USA

**Objective:** To evaluate the efficacy and safety of CVT-301 vs placebo, administered to Parkinson’s disease (PD) subjects during OFF periods.
**Background:** CVT-301 is being developed as a self-administered, inhaled therapy that delivers levodopa to the lungs, where it is rapidly absorbed into the circulation bypassing first-pass metabolism.[1] It is intended to treat OFF periods (re-emergence of Parkinsonian symptoms) for patients also taking an oral dopa-decarboxylase inhibitor/levodopa regimen.

**Methods:** This clinical trial was a 12-week, randomized, double-blind, placebo-controlled, multinational study of PD subjects experiencing motor fluctuations. Subjects receiving a stable regimen of oral carbidopa/levodopa were randomized 1:1:1 for placebo, CVT-301 84 mg, or CVT-301 60 mg up to 5 times daily. Subjects used study medication adjunctively with usual PD medications, to treat OFF periods, as needed. The primary efficacy endpoint was the change in UPDRS-III (motor) score at 30 min from pre- to postdose with CVT-301 84 mg vs placebo at week 12 when subjects were evaluated in-office during an OFF period. Key secondary endpoints: proportion of subjects achieving an ON state within 60 min of treatment and remaining ON at 60 min; change in UPDRS-III (motor) score at 10 and 20 min postdose; improvement in Patient Global Impression of Change Scale; total daily OFF time. Safety profile, including pulmonary function, was assessed.

**Results:** 339 subjects were randomized and received at least 1 dose of CVT-301 or placebo; 290 completed the study. Mean subject age was 63.3 years; 73.5% were male. Mean PD duration was 8.3 years and subjects received levodopa for a mean of 6.7 years. On average, subjects experienced 3.5 OFF periods daily (mean total OFF time: 5.5 hours). The UPDRS-III score change at 30 min for the 84-mg dose during the in-office evaluation was –9.8 vs –5.9 for placebo (P=.009; Figure). The most common adverse events for CVT-301 84 mg vs placebo were cough (14.9% vs 1.8%, reported once/subject), upper respiratory tract infection (6.1% vs 2.7%), nausea (5.3% vs 2.7%), and sputum discoloration (5.3% vs 0%). Spirometry data showed no significant pulmonary safety signals. Additional data will be presented.

![CVT-301 84 mg versus placebo: UPDRS-III from 0 min to 60 min postdose at week 12](image)

*Nominal P value < .05 vs placebo.*

**Conclusions:** In this 12-week phase 3 study, CVT-301 84 mg significantly improved motor function relative to placebo in PD subjects experiencing OFF periods. The CVT-301 84-mg dose was generally well tolerated.

Objective: To determine if untargeted biochemical profiling (metabolomic analysis) of small-molecule (<1.5 kDa) constituents of CSF and plasma can yield useful diagnostic biomarkers of PD.

Background: As PD is associated with systemic mitochondrial and other metabolic alterations, metabolomic analysis has the potential to recognize PD-specific patterns, offering diagnostic correlations and insights into the disease process.

Methods: Specimens came from BioFIND study* participants; PD subjects met rigorous diagnostic criteria and were symptomatic for >5 years. Standardized biospecimen procedures were used for collecting CSF and plasma from 50 HCs matched to 50 PD subjects. Assays involved ultrahigh-performance liquid chromatography linked to tandem mass spectrometry**. A spectral reference library provided chemical identifications. Data underwent intensive curation and quality-control measures. Each analyte was individually tested for t-test association with PD. False-discovery rate (FDR)-adjusted p-values were calculated. Least Absolute Shrinkage and Selection Operator (LASSO) logistic regression was used to identify a multi-metabolite profile that discriminated PD subjects from HCs.

Results: LASSO selected 23 biochemicals distinguishing PD from HCs with Area-Under-the-Receiver-Operating-Curve of 89.7%. With optimal cutoff, LASSO achieved 100% sensitivity and 96% specificity (with positive and negative predictive values of 96% and 100%). Ten-fold cross-validation gave 84% sensitivity and 82% specificity (with 82% positive and 84% negative predictive values). The top 3 coefficients from the regression model were for ornithine, N-acetylputrescine, and a compound that was either N-acetylglucosamine or N-acetylgalactosamine. In contrast to CSF, metabolomic analysis of plasma did not distinguish PD from HCs. In the univariate analysis (Figure), 21 CSF compounds were differentially expressed between PD and HCs (FDR <0.05). Metabolic pathway analysis of the LASSO-selected biomarkers was not informative.
Conclusions: Metabolomic profiling of CSF (but not plasma) provided strong prediction of PD versus HCs. Biomarkers discovered in this analysis may be useful at enhancing diagnosis of PD and for better understanding of its etiology.


LBA 36
Pridopidine, a clinical trial-ready compound, reduces L-DOPA-induced dyskinesia in the MPTP-lesioned macaque model of Parkinson’s disease

Tom Johnston, Michal Geva, Lilach Steiner, Aric Orbach, Spyros Papapetropoulos, Juha-Matti Savola, Ian Reynolds, Paula Ravenscroft, Michael Hill, Susan Fox, Jonathan Brotchie, Michael Hayden


Objective: To evaluate the potential of pridopidine to reduce established L-DOPA-induced dyskinesia (LID) in the MPTP-lesioned non-human primate model of Parkinson’s disease (PD) and define target plasma exposure levels to guide clinical development.

Background: Effective treatments for LID, a major complication of dopamine-replacement therapy in PD, remain a significant unmet need. A therapy that could suppress LID when combined with L-DOPA without reducing its benefit or worsening symptoms of the disease would be of great clinical utility. Pridopidine is an experimental therapeutic currently under late stage development for the treatment of Huntington disease. Pridopidine was originally classified as a ‘dopamine-stabiliser’ i.e. a low affinity (IC50 ~10 µM), fast-off, dopamine D2 receptor antagonist. Low affinities in the same micromolar range as the D2R were also found for other CNS targets with potential relevance to LID, such as the α2C receptor (IC50 3.56 µM), D3 receptor (IC50 4.79µM) and 5-HT1A receptor (IC50 6.36 µM). More recently, pridopidine has been shown to bind with high-affinity to the sigma-1 receptor (S1R) (IC50 ~100 nM). Pridopidine was shown to reduce L-DOPA-induced sensitisation (rotational behaviour) in the 6-OHDA-rat model suggesting a potential to mediate aberrant L-DOPA-induced behaviours such as LID. The aims of the current study were to investigate whether pridopidine could reduce LID in the MPTP-lesioned primate model of PD and to characterise the observed behavioural effects in terms of the in-vivo receptor occupancy (PET) and receptor binding profile of pridopidine.

Methods: Eight female cynomolgus macaques were rendered parkinsonian with MPTP. Stable and reproducible LID was established by repeated once-daily L-DOPA therapy. The actions of pridopidine (7 and 20 mg/kg, PO) on parkinsonism, dyskinesia and quality of on-time in combination with L-DOPA were evaluated for 6 h. For each animal, a dose of L-DOPA (range 30-35 mg/kg, PO) was defined as that providing an anti-parkinsonian benefit lasting ~3-4 h but compromised by severe, disabling levels of dyskinesia. The pharmacokinetic profile of pridopidine was also characterised in plasma samples collected at multiple time-points up to 24h after oral administration. These and other PK data across rodent and primate species were used to assess the relationship between plasma pridopidine levels and central S1R / D2/3R receptor occupancy.

Results: Pridopidine produced a dose-dependent reduction in peak-dose dyskinesia (both choreiform and dystonic in nature), by up to 76% (20 mg/kg) (P < 0.001). Pridopidine was largely ineffective in reducing LID at a dose of 7 mg/kg. L-DOPA alone produced a robust alleviation of parkinsonian disability such that median levels of parkinsonian disability were absent to mild though compromised by dyskinesia that were marked to severe during the first two hours following administration. Duration of total on-time associated with L-DOPA alone was 204 minutes of which 105 minutes (52% of total) was of ‘bad’ quality. After administration of the L-DOPA-pridopidine combination, dyskinesias were reduced to below mild, i.e. non-disabling. Pridopidine (20 mg/kg) also decreased the duration of ‘bad’ quality on-time evoked by L-DOPA by 46% (P < 0.01). This decrease was observed in the absence of any change to the total duration of on-time or extent of anti-parkinsonian benefit of L-DOPA.
Oral administration of pridopidine, 7 and 20 mg/kg, was associated with plasma Cmax of 2.3 and 7.7 µM respectively. Receptor occupancy using (i) known binding affinities of pridopidine to human and rodent S1R and D2R in vitro, (ii) in vivo PET imaging in rats, and (iii) pharmacokinetic profiling in the different species, showed that anti-dyskinetic effect of the higher dose (20 mg/kg) would correspond to high S1R occupancy (>80%) and moderate D2/3 receptor occupancies (30%). By contrast, plasma exposures observed following the lower, ineffective dose (7 mg/kg), while associated with S1R occupancy of 60-80%, would have only engaged D2/3 receptors in the 0-30% occupancy range.

Conclusions: In MPTP-lesioned NHPs, pridopidine produced a significant and meaningful decrease in LID without compromising the anti-parkinsonian benefit of L-DOPA. While we believe the anti-dyskinetic actions of pridopidine were associated with high S1R occupancy, effective exposures may be associated with occupancy of multiple non-sigma receptors, including α2C and 5-HT1A. This complex pharmacology may underlie the effectiveness of pridopidine against LID. Target plasma exposures for clinical development in LID might include Cmax of up to 10 µM (2.8 µg/mL).

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LBA 37
Inner retinal thinning correlates with nigral dopaminergic loss in de novo Parkinson’s disease

Jee-Young Lee, Jeeyun Ahn, Tae Wan Kim, Sohee Oh, Yu-Kyeong Kim, Jong Min Kim, Beomseok Jeon
Seoul National University Boramae Hospital and College of Medicine of Seoul National University Seoul, Korea

Objective: This study was primarily aimed to demonstrate inner retinal layer thinning in a consecutively recruited cohort of drug-naïve newly diagnosed Parkinson’s disease (PD) patients implying an automated segmentation analysis of single retinal layers and using an advanced statistical model taking into age, axial length, and within-subject inter-eye correlations altogether, and then secondarily to explore pathological implication of retinal thinning by performing a correlation analysis with ipsilateral nigral dopaminergic loss estimated by dopamine transporter PET imaging.

Background: Visual disturbance is a common nonmotor symptom of PD, and it is frequently noted from very early stages of the disease. There are reports in PD patients about decreased dopamine contents in the retina and abnormal retinograms that can be reversed with levodopa treatment. With advances in optical coherence tomography (OCT) technology, morphological changes in the foveal pit and retinal thinning was found in patients with PD. Recently, pathology reports revealed alpha-synuclein pathology in PD patients’ retina, mostly in the inner layers, but not in Alzheimer’s disease or control subjects. Alpha-synuclein overexpression fly model showed that retina could degenerate with overloading of alpha synuclein in the retina, thus suggesting a pathological link between retinal thinning and brain degeneration in PD. However, there has been no study exploring the correlation between the retina and dopaminergic loss in PD patients so far.

Methods: 60 drug-naïve PD patients who were newly diagnosed and consecutively enrolled, and 60 age-matched healthy controls were recruited for this study. All participants underwent thorough ophthalmologic examinations and perifoveal OCT scans in conjunction with microperimetry. PD patients additionally underwent dopamine transporter PET (18F-FP-CIT) and 3T MRI scans. Thickness of each retinal layer was measured in the whole scanned area by 9 sectors using automated segmentation software. Comparison between PD and controls was performed using a generalized estimating equation model adjusting for within-patient inter-eye correlation, and correlation between inner retinal thinning and with microperimetric response was examined. A possible correlation between each retinal layer thickness and dopamine transporter densities in the ipsilateral caudate, anterior and posterior putamen, and the substantia nigra was explored with linear regression analysis, and, then the significance of correlation was tested with implying the Generalized Linear Mixed Models (GLMM) taking into random effects of multiple retinal sectors and layers in each individual.

Results: Data from 49 (89 eyes, aged 68.9 years) PD patients and 54 (108 eyes, aged 70.6 years) controls were finally included in the analysis. In PD patients, significant retinal layer thinning was observed in the temporal and inferior sectors (p=0.010 for both), which was in the inner retinal layers including nerve fiber layer, ganglion cell
layer, and inner plexiform layer, particularly in near foveal zones. Thickness of inner retinal layers correlated positively with macular sensitivity. Inner retinal layer thickness correlated with dopamine transporter densities in the ipsilateral caudate, anterior and posterior putamen, and the substantia nigra by age and axial length-adjusted analyses (all p<0.05), and the correlation in the left substantia nigra was found to be significant by the GLMM (p<0.001).

Conclusions: Inner retinal structural changes in de novo Parkinson’s disease were associated with decreased macular sensitivity and dopaminergic neuronal loss in the brain. Retinal structural change may act as an important window for neuronal degeneration and is a potential biomarker for Parkinson’s disease. The pathophysiology of brain-retina interconnection in Parkinson’s disease is worth being investigated.

LBA 38
Chronic intake of Mucuna pruriens in advanced Parkinson’s disease: A non-inferiority, randomized, crossover, pilot study

Roberto Cilia, Janeth Laguna, Erica Cassani, Emanuele Cereda, Benedetta Raspini; Michela Barichella; Gianni Pezzoli

Parkinson Institute, ASST Pini-CTO; Neurology Clinic; Clinica Niño Jesus, Santa Cruz, Bolivia
Milan, Italy; Santa Cruz, Bolivia

Objective: To investigate safety and efficacy of daily intake of Mucuna pruriens (MP) powder as compared to marketed levodopa/carbidopa over a 16-week period using a crossover study design.

Background: Thousands of individuals with Parkinson’s disease (PD) in low-income countries remain either undertreated or untreated due to unaffordability of marketed levodopa preparations. MP, a levodopa-containing leguminous plant growing in all tropical areas worldwide, may be a sustainable alternative therapy for indigent patients.

Methods: Fourteen patients with advanced PD (mean age 61±10 years, disease duration 9.4±2.7 years) received MP powder (obtained from roasted seeds) and marketed levodopa/carbidopa (LD/CD) in a randomised order and crossover design over a 16-week period. Efficacy measures were changes in quality of life, activities of daily living, motor and non-motor symptoms, and time with good mobility without troublesome dyskinesias. Safety measures were frequency of adverse events, changes in laboratory indices and electrocardiography. Considering the limited sample size and exploratory nature of this study, we used an arbitrary cut-off of p-value >0.5 to set the margin for non-inferiority. This study is registered at ClinicalTrials.gov, NCT02680977.

Results: In the intention-to-treat population, MP was non-inferior to LD/CD in all efficacy measures, including quality of life. Seven discontinued MP treatment due to either reduced tolerability (n=4/7) or progressive worsening of motor performance (n=3/7). At baseline, patients who discontinued MP were more depressed and showed milder OFF-state motor symptoms than those who completed the protocol. At per-protocol analysis, MP showed a trend for better outcome than LD/CD in all efficacy measures.

Conclusions: Chronic intake of MP powder was non-inferior to marketed LD/CD preparations in terms of efficacy. Further studies are warranted to increase MP tolerability in the long-term and identify appropriate titration schemes and maintenance daily dose.
Noradrenergic deficit in Parkinson’s disease patients with REM sleep behavior disorder is linked to cognitive performance – A 11C-MeNER PET & neuromelanin MRI study


Department of Nuclear Medicine and PET Centre, Aarhus, Denmark; Department of Clinical Medicine & Department of Psychology, Aarhus, Denmark; Department of Clinical Neurophysiology, Aarhus, Denmark

Objective: To study the noradrenergic system and its relation to cognitive performance using 11C-MeNER as a PET ligand for the noradrenaline transporter and neuromelanin sensitive MRI of the locus coeruleus-subcoeruleus complex (LC) in Parkinson’s disease (PD) patients with and without REM sleep behavior disorder (RBD).

Background: RBD in PD is increasingly recognized as a PD phenotype with unfavorable disease course, higher burden of non-motor symptoms and particularly increased risk of cognitive decline. Noradrenergic innervation arising from neuromelanin-containing cells in the LC is a key modulator of cognition and sleep-wake regulation. These cells are believed to be affected early in PD genesis; however, their relation to RBD and cognition in PD remains to be elucidated.

Methods: Eleven non-demented and non-depressed PD -RBD (64±8.9y, 4 females, H&Y 2.0) and 13 PD +RBD (69±8.8y, p=0.204, 4 females, p=1, H&Y 2.4, p=0.165) underwent imaging with neuromelanin sensitive MRI of the LC and 90min dynamic 11C-MeNER PET of the brain. Distribution volume ratios (DVRs) were calculated with the Simplified Reference Tissue Model 2 (SRMT2) using the caudate as reference. Regional DVRs were assessed in 6 noradrenaline transporter rich regions (thalamus, hypothalamus, red nucleus, LC, dorsal raphe, median raphe) and compared to age and sex matched control samples (n=7). RBD was ascertained with overnight polysomnography; REM sleep without atonia was calculated from the chin EMG (tonic: 2x baseline for >15s per 30s epoch, phasic: >4x baseline on 3s epochs, any: tonic and/or phasic on 3s epochs). Polysomnography included resting EEG with power spectral analysis. Cognitive performance was assessed with a test-battery adhering to the 2012 MDS diagnostic criteria for mild cognitive impairment (MCI) in PD with z-score thresholds set at 1.5.

Results: Repeated measures ANOVA of 11C-MeNER DVRs revealed a significant group effect (p<0.001) and significance between all 3 groups in post-hoc testing (PD +RBD vs PD -RBD p=0.002, PD +RBD vs controls p<0.001, PD -RBD vs controls p=0.033; Figure A); PD +RBD patients displayed lowest DVRs, most pronounced in brainstem nuclei. PD +RBD patients also showed lowest LC-to-pons ratio in neuromelanin-sensitive MRI (univariate ANOVA p=0.001, PD +RBD vs PD -RBD p=0.045, PD +RBD vs controls p<0.001, PD -RBD vs controls p=0.016; Figure B). Amount of REM sleep without atonia correlated with 11C-MeNER DVR of the LC but not with MR neuromelanin contrast (Pearson’s r=-0.591, p=0.003 for all PD patients and r=-0.602, p=0.038 for PD +RBD; Figure C). Alpha/theta ratio on waking EEG was lower in PD +RBD compared to PD -RBD patients (4.89 vs 2.05, p=0.016, unpaired t-test), and 11C-MeNER DVR of the LC correlated with alpha/theta ratio as well as with background frequency (Pearson’s r=0.522, p=0.013 and r=0.549, p=0.008; Figure D). MCI was more frequent in PD +RBD compared to PD -RBD (46% vs 18%, chi-square p=0.148) and global cognitive performance correlated with 11C-MeNER DVR of the LC (Pearson’s r=0.494, p=0.014; Figure E).

Conclusions: PD patients with RBD showed marked reductions of neuromelanin MRI contrast and 11C-MeNER PET signal. The 11C-MeNER signal decrease suggests noradrenergic denervation, and was associated with amount of altered muscle activity during REM sleep, electroencephalographic slowing and cognitive deterioration.
Figure A

Distribution Volume Ratios (DVR) of 11C-MeNER PET in 6 Norepinephrine Transporter rich regions. P-values of region-wise comparisons are given as following:

*** p<0.005, ** p<0.01, * p<0.05, ns: not significant

Figure B

LC to Pons ratio of T1-weighted turbo spin-echo MRI; *** p=0.005, ** p<0.01, * p<0.05

Figure C

Correlation of 11C-MeNER signal in the LC with amount of REM sleep without atonia

Figure D

Correlation of 11C-MeNER signal in the LC with EEG background frequency

Figure E

Correlation of 11C-MeNER signal in the LC with global cognitive performance (average of z-scores of all 5 domains)
First results from the TWEED-study: Directional DBS increases side effect thresholds

Till A. Dembek, Paul Reker, Veerle Visser-Vandewalle, Jochen Wirths, Harald Treuer, Martin Klehr, Jan Roediger, Haidar S. Dafsari, Michael T. Barbe, Lars Timmermann

Department of Neurology and Department of Stereotactic and Functional Neurosurgery
Cologne, Germany

Objective: To investigate whether directional DBS of the subthalamic nucleus in Parkinson’s disease (PD) offers increased therapeutic windows, side effect thresholds and clinical benefit.

Background: Directional leads have been the most recent technological step in the development of new deep brain stimulation (DBS) paradigms.

Methods: Twenty, prospective, randomized and double blind monopolar reviews were conducted in ten PD patients with directional leads to identify the best stimulation direction. Results regarding side effect thresholds, width of the therapeutic window, and therapeutic efficacy were compared to circular DBS on the same lead level.

Results: Stimulation in the individual best direction significantly increased the therapeutic windows mainly due to a significant increase in side-effect thresholds [Figure]. While improvement in rigidity and finger tapping did not differ between directional and circular DBS, hand rotation showed an overall higher improvement during directional DBS.

Conclusions: Directional DBS can increase side effect thresholds while achieving short-term clinical benefit comparable to or even slightly better than conventional DBS. However it remains unclear, whether these results will translate to improved long term outcome.
LBA 41
Safety, efficacy and tolerability of continuous SC LD/CD (ND0612) infusion in PD patients with motor fluctuations

C. Warren Olanow, Aaron Ellenbogen, Ruth Djaldetti, Tamar Rachmilewitz Minei, Yael Cohen, Sheila Oren, Karl Kieburtz
Clintrex, Rye, NY, USA; Michigan Institute for Neurological Disorders, Farmington, MI, USA; Tel Aviv University, Tel Aviv, Israel; NeuroDerm, Rehovot, Israel.

Objective: Evaluate the safety, efficacy and tolerability of 2 dosing regimens of ND0612, a continuous subcutaneous (SC) L-dopa/carbidopa (LD/CD) infusion.

Background: ND0612 is a proprietary LD/CD liquid solution designed for continuous SC infusion.

Methods: This was a 28-day randomized, parallel-group, open label, blinded-rater study. Subjects with fluctuating PD were randomized (1:1) to two dosing regimens of ND0612: R1 (24h infusion with 720/90 mg LD/CD) or R2 (14h ‘waking-day’ infusion with 538/68mg LD/CD + morning oral LD/CD 150/15 mg). Supplemental oral LD/CD was used as needed. Primary and key secondary efficacy endpoints were change from baseline to Day 28 in daily OFF time (blinded rater 8h observation normalized to 16h day) and change from baseline in % of subjects with full ON at 8 & 9 AM.

Results: Of the 38 randomized subjects (mean age: 63.5y; disease duration: 11.5y; Mean OFF time 5.3h/day), 33 (87%) completed the study. The R1 group met the primary endpoint (mean reduction in OFF-time of 2.8h, p=0.004); 8 of 19 (42%) subjects had a complete reduction in OFF time to 0 hours. The proportion of subjects with full ON was significantly increased at both timepoints (8AM: 11% to 50%, p=0.02; 9AM: 26% to 75%, p=0.004). 'Good' ON time (no or mild dyskinesia) increased by a mean of 3.7h (p<0.001). In R2, mean reduction in OFF time was 1.3 h (NS); 11% had a complete reduction in OFF time to 0 hours. There were no significant changes in the key secondary measures. Improvement in good ON time was 2.8h (p=0.003). Mean oral LD dose decreased from 1100 to 344mg. The most frequent AEs were mild-moderate infusion-site reactions: nodules (42%), bruising (18%) and erythema (16%). One subject discontinued due to infusion site abscess & another due to PD symptom worsening. Both regimens were well tolerated.

Conclusions: In this Phase 2 study both regimens were well tolerated. The 24h infusion significantly reduced daily OFF time while increasing morning ON time and total daily good ON time. R2 did not provide optimal dosing for ND0612 but still showed a significant improvement in good ON time. A longer daytime regimen of 16h (LD/CD 720/90 mg) starting immediately upon waking up is under evaluation. These findings suggest that ND0612 SC infusion can provide important benefits for advanced PD patients without the risks associated with a surgical procedure.

LBA 42
Multi-electrode subthalamic, pallidal, and thalamic recordings in children and young adults with secondary dystonia show widespread activation correlated with dystonic muscle contractions

Terence Sanger, Mark Liker, Enrique Arguelles, Arash Maskooki, Diana Ferman, Aaron Robison
University of Southern California
Los Angeles, CA, USA

Objective: To describe the pattern of activity associated with dystonic movement in subthalamic nucleus, globus pallidus, and ventrolateral nuclei of the thalamus in children with secondary dystonia.

Background: Very little is known about the patterns of neural activation responsible for dystonic muscle contractions in children with secondary dystonia. While it is likely that similar mechanisms exist between primary
and secondary dystonia, the variability of symptomatology and etiology in secondary dystonia suggests corresponding differences in the location or patterns of activation.

**Methods:** 7 children and young adults ages 6-20 undergoing exploration of basal ganglia and thalamus to determine targets for deep-brain stimulation insertion were investigated. Diagnoses included perinatal hypoxic-ischemic injury, striatal necrosis, and kernicterus. Each child had between 6 and 10 temporary electrodes implanted and externalized for 1 week in multiple regions, and each electrode had 10 micro-contacts capable of identifying single cell firing activity, and 6 macro-contacts capable of identifying local field potentials. Custom cell-sorting algorithms identified between 1 and 5 independently-firing cells at each micro-contact, so that children typically had between 100 and 500 simultaneously-recorded cells. Cell activity was recorded with children awake in a hospital bed, performing voluntary reaching, hand, finger, leg, or foot movements, and in some cases during speech, sitting, or walking. Surface electromyography (sEMG) was recorded from up to 8 muscles of the arms or legs.

**Results:** Activity patterns varied between children. Dystonic contractions on sEMG correlated most commonly with widespread activity in contralateral globus pallidus, but in some children also correlated with activity in one or more of contralateral VLa, VLp[Vim], or VPL thalamic nuclei, and in one patient STN. In 3 children, contractions were correlated with ipsilateral neural activity. Passive movement of a dystonic limb generated widespread high activity in contralateral VPL in one child.

**Conclusions:** Widespread and unfocused activity within thalamus and basal ganglia appears to be characteristic of secondary dystonia. Unlike primary dystonia, the location of activity in secondary dystonia varies between children. These results suggest that the target for deep-brain stimulation may need to be carefully selected to reflect the varying anatomic origins of dystonia in children with different underlying etiologies.

**LBA 43**

Atrophy characteristics and associations with clinical measures in preclinical and manifest spinocerebellar ataxia type 2

*Kathrin Reetz, Roberto Rodriguez-Labrada, Imis Dogan, Shahram Mirzazade1, Sandro Romanzetti1, Jörg B. Schulz1, Edilia M. Cruz-Rivas2, Jose A. Alvarez-Cuesta2, Raul Aguilera Rodríguez2, Yanetza Gonzalez Zaldivar2, Georg Auburger3, Luis Velázquez-Pérez2*

1Department of Neurology, RWTH Aachen University, Aachen, Germany; 2 Department Clinical Neurophysiology, Centre for the Research and Rehabilitation of Hereditary Ataxias, Calle Libertad 26, Holguín, Cuba, 80100, Cuba; 3 Experimental Neurology, Goethe University Medical School, 60590 Frankfurt/Main, Germany

**Objective:** To evaluate atrophy characteristics and associations with clinical measures in preclinical and manifest spinocerebellar ataxia type 2.

**Background:** Spinocerebellar ataxia type 2 (SCA2) is an autosomal dominantly inherited disease characterized by progressive degeneration of the nervous system, mainly affecting the cerebellum and brainstem.

**Methods:** In this Cuban-German research collaboration, 16 non-manifest SCA2 mutation carriers, 26 manifest patients with SCA2 and 18 age- and gender-matched controls underwent magnetic resonance imaging as well as genetic and clinical characterization including motor assessment, neuropsychology and saccade velocity in Cuba. Semi-automated, quantitative three-dimensional volumetry of the cerebellum and the brainstem, subdivided into the medulla oblongata, the pontine brainstem and mesencephalon was performed and volumes were normalized to the total intracranial volume. Additionally the antero-posterior diameter of the pontine brainstem was measured.

**Results:** Analysis of volumetric data revealed volume loss of the brainstem (including pontine brainstem and mesencephalon) and the cerebellum in individuals at risk for SCA2 compared to controls. Preclinical SCA2 mutation carriers also showed reductions of the antero-posterior diameter of the pontine brainstem. In manifest SCA2 patients, we observed volume reductions of the brainstem, specifically of the pontine brainstem and pontine diameter, and cerebellum compared to controls. Comparing patients with non-ataxic preclinical SCA2 mutation
carriers, we found more pronounced reductions of both the pontine brainstem and cerebellum in manifest SCA2. Volumetric data further showed associations with CAG repeat length and predicted age of onset in preclinical SCA2 individuals, and by trend with ataxia signs in patients. Whereas saccade velocity was associated with reduction of the pontine brainstem volume, reduced ability to suppress interfering stimuli measured by the Stroop task was related to reduced cerebellar volume.

Conclusions: Preclinical SCA2 mutation carriers exhibit brain abnormalities, which could be targeted in future preventive trials in this early disease stage.

LBA 44
Blood pressure data and variability in individuals with de novo Parkinson’s disease enrolled in the STEADY PD III trial

Christopher G. Tarolli 1,2, Robert G. Holloway 1, Jamie L. Adams 1,2, Kevin M. Biglan 1,3, John D. Bisognano 4, Brittany Greco 1, Karen Hodgeman 2, Sam Lerman 2, Nick Potter 2, Charles Venuto 1,2, Tanya Simuni 5

1 Department of Neurology, University of Rochester; 2 Center for Human Experimental Therapeutics, University of Rochester; 3 Early Phase Clinical Development, Neurosciences, Eli Lilly and Company; 4 Department of Internal Medicine, Cardiology Division, University of Rochester; 5 Department of Neurology, Northwestern University 1,2,3,4 Rochester, NY, USA; 5 Chicago, IL, USA

Objective: To characterize blood pressure (BP) and heart rate (HR) variability collected remotely in a cohort of individuals with early Parkinson’s disease (PD).

Background: PD can be associated with autonomic instability, and orthostatic hypotension (OH) has been associated with more rapid disease progression. However, limited data exist on the prevalence of autonomic instability in the de novo PD population. Here, we present data on BP and HR variability in a group of individuals with early PD not receiving dopaminergic therapy, enrolled in a clinical trial.

Methods: STEADY-PD III is a phase 3, double-blind, placebo-controlled trial of the efficacy, safety, and tolerability of isradipine (a dihydropyridine calcium channel antagonist) for PD. Enrolled individuals were provided with a digital BP monitor that allowed remote collection and evaluation of BP and HR. Central BP monitoring was provided by Carematix, Inc. Participants were asked to obtain sitting and standing readings twice daily for at least 7 days prior to initiation of study drug and during titration. Readings taken before study drug initiation are described here. Orthostasis was defined as a decrease in systolic BP by ≥20mmHg, diastolic BP by ≥10mmHg, or increase in HR by ≥20bpm from sitting to standing.

Results: 336 individuals were enrolled with data captured in 332 participants. Mean pairs of readings per participant were 30. Median sitting and standing systolic BPs, diastolic BPs, and HRs were 128 and 126mmHg, 77 and 80mmHg, and 70 and 77bpm, respectively. 16.3% of readings met criteria for OH, with 267 (80.4%) participants having at least one reading that met these criteria. 30 (9.0%) participants met criteria for OH in ≥50% of readings.

Conclusions: Our data indicate that intermittent OH is common in a group of individuals with early untreated PD. However, only a minority of individuals demonstrate consistent OH. It is unclear if these individuals represent a group with PD and early autonomic instability, or whether an alternative diagnosis like multiple system atrophy should be considered. Ongoing longitudinal evaluation will help to define the ultimate diagnosis, the natural history of autonomic dysfunction in PD, and the potential utility of OH as a vasomotor biomarker of PD progression.
LBA 45
Predictive accuracy of the MDS research criteria for prodromal Parkinson’s disease in the general elderly population and their utility as a tool to define target cohorts for neuroprotection trials

Philipp Mahlknecht, Arno Gasperi, Atbin Djamshidian, Stefan Kiechl, Heike Stockner, Johann Willeit, Gregorio Rungger, Werner Poewe, Klaus Seppi

Department of Neurology, Innsbruck Medical University
Innsbruck, Austria

Objective: We aimed at assessing the predictive accuracy of prodromal Parkinson’s disease (PD) as per Movement Disorder Society (MDS) research criteria for incident PD in the elderly population over 10 years and at deriving sample-size estimations for neuroprotection trials.

Background: Recently, a MDS task force has published research criteria for the prodromal phase of PD. These criteria are based on a data driven probabilistic approach using a Bayesian naïve classifier methodology assuming a 10-year prodromal period.

Methods: We retrospectively applied the MDS criteria for prodromal PD to participants of the prospective population-based Bruneck Study at the 2005 assessment (n=574; age 55–94 years). Cases of incident PD, anchored on the United Kingdom PD Society Brain Bank criteria, were identified at a 3-year, 5-year and a very recent 10-year follow-up visit. Based on the observed distribution of incident cases we calculated sample sizes for interventional neuroprotection trials.

Results: At baseline 12 participants were identified with probable prodromal PD. During follow-up 6 participants were identified with incident PD at 3 years, 11 at 5 years, and 20 at 10 years (cumulative). A diagnosis of probable prodromal PD had a specificity in predicting incident PD of 99%, a sensitivity of 67%, and a positive predictive value (PPV) of 40% over 3 years. Specificity remained stable with increasing follow-up time, sensitivity decreased to 55% over 5 years and to 35% over 10 years, and PPV rose to 60% and 78%, respectively. Sample size estimates ranged from 108 to 540 subjects with probable prodromal PD needed for trials with a primary outcome of conversion to clinically defined PD at 80% power depending on trial duration (3–5 years) and effect size of the agent (30%–50%).

Conclusions: Our findings suggest that the MDS research criteria are a promising tool to identify cases of incident PD in the general elderly population. After validation in independent prospective cohorts, future neuroprotection trials may successfully use these criteria for the definition of target populations.

LBA 46
Pridopidine has neuroprotective and neurorestorative effects in a mouse model of nigrostriatal dopamine degeneration

(1) Veronica Francardo, (2) Michal Geva, (2) Michael Hayden, (1) M.Angela Cenci

(1) Basal Ganglia Pathophysiology Unit, Department of Experimental Medical Science, BMC F11, Lund University/(2) Teva Pharmaceutical Industries Global Research and Development (1) Lund, Sweden/(2) Netanya, Israel

Objective: The aim of the study is to investigate potential neuroprotective and neurorestorative effects of pridopidine in a mouse model of nigrostriatal dopamine degeneration relevant to Parkinson’s disease (PD).

Background: We have recently demonstrated that pharmacological stimulation of the Sigma-1 receptor promotes recovery of motor functions and activates neuroplasticity in the damaged nigrostriatal system (Francardo et al. Brain 2014, PMID 24755275). The Sigma-1 receptor is a chaperone protein at the mitochondrion-associated endoplasmic reticulum membrane, stimulating defence mechanisms under conditions of cellular stress. Pridopidine (now in
clinical studies for Huntington’s disease) has been classified as a ‘dopamine stabiliser’ with selectivity for dopamine D2 receptors, but it also binds with high affinity to the Sigma-1 receptor.

**Methods:** Mice with intrastriatal 6-hydroxydopamine (6-OHDA) lesions and sham-lesion controls received pridopidine (0.3 or 1 mg/kg/day) or vehicle for 35 days, starting on the same day as the lesion. Behavioral tests for spontaneous rotational asymmetry and forelimb use asymmetry (cylinder test and stepping test) were used once per week in order to monitor the effects of the compound during the treatment period. Brains were then prepared for immunohistochemical quantification of nigral dopaminergic cell bodies and striatal dopaminergic fibers density. The same experiment is now ongoing in Sigma-1 receptor knockout mice, to assess the target specificity of the observed effects.

**Results:** 6-OHDA-lesioned mice chronically treated with pridopidine showed gradual amelioration of PD-like motor deficits in tests of spontaneous rotational and forelimb use. Stereological cell counts revealed significant (22%) increase in the number of nigral tyrosine hydroxylase-positive neurons in the group treated with 0.3 mg/kg/day pridopidine. Analysis is ongoing to quantify the density of dopaminergic fibers in the caudate-putamen.

**Conclusions:** Our results show significant neuroprotection of dopaminergic neurons accompanied by substantial motor recovery in 6-OHDA-lesioned mice treated with the lower dose of pridopidine. It is warranted to consider further investigation of pridopidine for disease-modifying treatments in PD.

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**LBA 47**

**Satisfaction and impact on quality of life in patients with essential tremor treated with High Intensity Focused Ultrasound (HIFU) thalamotomy**


**Background:** Tremor has a well-known impact on several domains of QOL. Thalamotomy (by HIFU) is known to ameliorate postural tremor significantly but no data is available regarding its impact on QOL.

**Methods:** We evaluated QOL and satisfaction with the treatment with:
- Fahn-Tolosa scale part C and Clinical Global Impression (CGI)( neurologist);
- QUEST (QOL), HADS (anxiety and depression), CVG, ECSIT and modified TSQM 1.4 (satisfaction with treatment) and CGI(self-administered by patients
- Zarit (caregiver burden), HADS, EQ-5D- 5L and CGI(caregiver)

**Results:** Twenty-four patients were included in the study. Fahn-Tolosa scale showed a significant improvement (p<0.05), specially in Physical and Psychosocial domains. With regard to the CGI, patients, neurologists and the primary caregivers reported an improvement of tremor after HIFU.

**Conclusions:** HIFU thalamotomy improves QOL and reduces disability in all daily life activities as assessed by the Fahn-Tolosa part C. Patients, caregivers and neurologists considered that HIFU treatment improved disease severity. Longer follow-up is needed in order to determine long-term benefits of HIFU thalamotomy.
2017 MDS STUDY GROUP ABSTRACTS

**SG 01**
Assessment of pain in Parkinson’s disease: Comparison between clinical and self-reported measures


**Objective:** To compare the performance of several pain measures, self- and rater-based, in PD patients.

**Background:** Pain is a prevalent and complex symptom in Parkinson’s disease (PD). Several scales are available to assess pain in PD, including patient-reported outcomes and rater-based scales, such as the King’s Parkinson’s Disease Pain Scale (KPPS).

**Methods:** Data were extracted from the KPPS validation study (Chaudhuri et al, 2015). Pain assessment was made by self-administered (visual analogue scale –VAS- for pain, and EQ-5D and PDQ-8 items for pain), and rater-based measures (KPPS and NMSS item for pain). Other validated rating scales for PD symptoms assessment were also applied. Data analysis included correlation coefficients, comparison of pain scores between groups according to variables of interest and multivariate linear regression models with KPPS and VAS-pain as dependent variables.

**Results:** The sample was composed by 178 PD patients with non-explained pain. Mean age was 64.38 years (SD: 11.38) and disease duration, 5.4 (SD: 4.93). Patients were mainly in HY stage 2 (47.7%). Correlation coefficients between pain scales were low to moderate: from 0.21 (NMSS item 27 with KPPS) to 0.54 (KPPS with VAS-pain). KPPS obtained the highest correlation coefficients with the rest of measures: 0.64 with PDSS and 0.59 with NMSS. VAS-pain correlated 0.51 with global severity of PD (CISI-PD). All measures of pain showed the highest scores in patients with longest disease duration. Only KPPS and VAS-pain showed significant differences according to disease severity (HY). No significant differences in pain scores were found in relation to sex, age and age at onset. In the regression models, KPPS and VAS-pain showed associations with sleep disorders and motor symptoms, controlling for other variables.

**Conclusions:** Pain measures KPPS and VAS-pain showed the strongest associations with other clinical variables in PD. Our results suggest that pain assessment in PD should be done with a combination of rater- and patient-based measures.

**SG 02**
A global survey of the use and linguistic translation of the NMSQuest and NMSScale: implications for non-motor studies in Parkinson’s disease


**Objective:** To collect details of linguistic validations and translations of the non-motor symptoms questionnaire (NMSQuest) and non-motor symptoms scale (NMSScale) globally.

**Background:** The patient completed Parkinson’s disease (PD) NMSQuest and the health-professional completed NMSScale were validated since 2006 and recommended by the MDS and other learned societies for holistic assessment of NMS and their burden. The global range of these tools have not been properly evaluated.

**Methods:** A specific protocol was developed for a global survey involving relevant members of the MDS Non-Motor-Parkinson’s disease-Trainee Junior Subgroup. All reviewed literature, conducted interviews with international collaborators and Mapi was contacted (http://mapigroup.com/) to capture available translations of the NMSQuest and NMSScale.
Results: Translations of NMSQuest were available using linguistic validation in Dutch, French, German, Greek, Italian, Japanese, Malay, Chinese (mandarin), Spanish and Swedish. Investigator translated use of NMSQuest was reported from Thailand, India and Brazil. The NMSScale underwent linguistic validation in Danish, French, German, Italian, Norwegian, Spanish and Swedish. Translated use was reported in Malay, Chinese, Arabic and Brazilian (Portuguese). NMSScale has been used as an outcome measure in several industry-sponsored clinical trials (e.g. Abbvie, Britannia, Lundbeck, Pfizer, Cynapsus, UCB among others). Translations for oral administration of both tools are reported from Arab states, Korea, Egypt, India, Turkey, Taiwan, Tanzania, Nigeria and Mali.

Conclusions: The use of NMSQuest as a flagging tool and NMSScale as a grading holistic measure of NMS in PD indicates the global reach of these instruments which should be regarded as an essential quality standard for assessment of PD in clinic. Furthermore, they should be routinely included in relevant clinical trials and as such it is crucial that these tools are properly validated in different languages.

SG 03
Parkinson’s disease phenotype across different ethnic groups: comparison of non-motor symptoms in patients living in the United Kingdom and Mexico

A. Sauerbier, M. Rodriguez Violante, A. Cervantes Arriaga, A. Rizos, D. Trivedi, P. Martinez-Martín, M. Parry, M. Rosa-Grilo, R. Brown, K. R. Chaudhuri (London, United Kingdom)

Objective: The aim is to compare and contrast clinical profiles between UK-White Caucasian (UK-WC), UK-Asian, UK-Black African Caribbean (UK-BAC) and Mexican people with Parkinson's disease (PD) (PwP).

Background: Ethnic differences in PD phenotype (particularly non-motor symptoms (NMS)) are poorly understood.

Methods: Demographics as well as motor, quality of life and non-motor data assessed with validated tools were recorded, as well as nutrition habits.

Results: The mean demographics and results are shown in table 1. Demographics differ between groups with a lower mean age and mean age at onset in the Mexican group and more males in the UK-Asian group. UK-Asian and UK-BAC and Mexican PwP had higher NMSScale (NMSS) total scores compared to UK-WC PwP. The UK-BAC and UK-Asian patients reported worse quality of life compared to the UK-WC and Mexican cohort. The UK-WC PwP consumed more alcohol (mean units per day 5.3±9.4) compared to UK-Asian (2.19±4.5), UK-BAC (0.4±1.1) and Mexican PwP (0.3±0.9).
Conclusions: These preliminary findings suggest that clinical profiles may possibly differ across different ethnic groups. We are now exploring the detailed presentation as well as underlying mechanisms.

SG 04
Long-term levodopa therapy accelerates the circadian rhythm dysfunction in 6-OHDA rat model

D. Lv, Y. Wang, F. Wang, X. Zhang, X. Gu, Y. Yang (Suzhou, People’s Republic of China)

Objective: We aimed to study the effect of L-DOPA on circadian rhythms in 6-OHDA lesioned rats, and to clarify whether the disturbance of the circadian system in PD patients was associated with the disease progression itself, or the long-term L-DOPA replacement therapy.

Background: Parkinson disease (PD) patients with long-term L-DOPA treatment are suffering from circadian rhythm abnormalities, including impaired sleep-wake cycles, disrupted fluctuations of temperature, blood pressure, heart rate, hormonal levels and many other biological processes.

Methods: PD model was constructed by a bilateral stereotaxic injection of 6-OHDA into the striatum. 21 days later, the rats received intraperitoneal administration of saline or 25mg/kg of L-DOPA once daily for another 21 consecutive days. Rotarod test, footprint test and open field test were carried out to evaluate the motor function. Next, we collected SCN, striatum, cortex, liver and plasma at ZT4 (Zeitgeber Time), ZT10, ZT16, ZT22. Quantitative
PCR was used to analyze the mRNA levels of Clock, Bmal1, Per2, Rora; ELISA detected the levels of melatonin and cortisol; HPLC analyzed the expressions of D1R, D2R in striatum and cortex.

**Results:** Daily injection of L-DOPA alleviated the motor deficits induced by 6-OHDA lesions. And then, we observed the expression of different clock genes in different tissues. After L-DOPA treatment, compared with 6-OHDA group. The rhythm of Clock was abolished and phase of Per2 was reversed from a nocturnal to a diurnal pattern in SCN compared with 6-OHDA group. In striatum, the expression of Bmal1, Rora was lower than that in the 6-OHDA group at ZT10, but the amplitude of Clock was elevated in cortex at four time points in L-DOPA group. In liver, L-DOPA unaltered did not affect the rhythmicity and levels expression of the four clock genes; in addition, secretion of the cortisol secretion was increased and melatonin was further inhibited after L-DOPA treatment at ZT22. Furthermore, the expression of D2R was decreased in the striatum in of 6-OHDA lesions lesioned rats but D1R remained unchanged unaltered in cortex.

**Conclusions:** Our research indicated that severe performance in circadian system of advanced PD patients owing to not only the progressive degeneration of the disease, but also the continuous L-DPOA treatment.

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**SG 05**

**Self-rated burden grading of non-motor symptoms identifies landmarks and subtypes of Parkinson’s disease: First report from a Moscow-Madrid-London collaboration**

*N. Titova, S. Cankaya, F. Spinnato, E. Katunina, P. Martinez-Martin, M. Qamar, K.R. Chaudhuri* (Moscow, Russia)

**Objective:** To describe clinical and imaging biomarkers of non-motor symptoms burden (NMSB) as defined by NMS questionnaire (NMSQ) scores in a prospective international cohort study of Parkinson’s disease (PD).

**Background:** NMS are integral to PD and NMSB grading is now validated using NMSQ (1). Relationship of self-declared NMSB with objective biomarkers of PD has not been studied before.

**Methods:** 179 patients (68.5±11.4 yrs) have been studied (disease duration 7.29±6.85 yrs, 7% drug-naive, median Hoehn Yahr ((HY) 2). Measures of motor state, sleep, depression, anxiety, quality of life (QoL), Datscan and olfaction were collected.

**Results:** 17% were NMSB mild, 30% moderate, 26% severe, 26% very severe. 12% had very severe and 16% severe NMSB inspite of mild HY. Motor dysfunction was worse in very severe NMSB. Significant deterioration was seen with anxiety (mild 6.1 vs very severe 11) and QoL (mild 5.1 vs very severe 16). PD sleep scale total score worsened significantly with increasing NMSB. Datscan putamen uptake ratios were non-significant between NMSB (Table 1) in contrast to HY (Figure 1). Olfaction was significantly worse in very severe (70%) vs severe (32%), moderate (17%) and mild (13%).

<table>
<thead>
<tr>
<th>NMS score</th>
<th>NMSB</th>
<th>N</th>
<th><strong>DATscan Uptake ratio (Normal &gt;2)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right Putamen</td>
</tr>
<tr>
<td>0-5</td>
<td>Mild</td>
<td>31</td>
<td>0.93</td>
</tr>
<tr>
<td>6-9</td>
<td>Moderate</td>
<td>54</td>
<td>1.06</td>
</tr>
<tr>
<td>10-13</td>
<td>Severe</td>
<td>47</td>
<td>0.75</td>
</tr>
<tr>
<td>&gt;13</td>
<td>Very Severe</td>
<td>47</td>
<td>0.92</td>
</tr>
</tbody>
</table>
Conclusions: Self-declared NMSB grading is capable of identifying subgroups of NMS dominant phenotypes. Very severe NMSB is characterised by olfactory, sleep and anxiety disorders but relatively retained putaminal dopamine transporter uptake.

SG 06
Long-term effects of subthalamic nucleus deep brain stimulation on quality of life, non-motor and motor symptoms


Objective: To study the long-term effects of bilateral subthalamic deep brain stimulation (STN-DBS) on Quality of Life (QoL), motor, non-motor symptoms (NMS) in patients with Parkinson’s disease (PD) using validated composite measures.

Background: Class I evidence shows that STN-DBS improves motor symptoms and QoL in patients with PD. However, only few studies have investigated non-motor effects of DBS, in particular its long-term effects. We hypothesized that STN-DBS is associated with a reduction of a range of NMS in patients with PD.

Methods: In this ongoing, multicenter, open, prospective, international study (London, Cologne, Manchester) we investigated non-motor effects of STN-DBS in real-life use in patients with PD. We surveyed PD Quality of Life Questionnaire (PDQ-8), Non-motor Symptoms Scale (NMSS), Non-motor Symptoms Questionnaire (NMSQ), and Scales (ADL, motor examination, and complications) at preoperative baseline, at 6 months follow-up (6MFU) and 24 months FU (24MFU).

Results: Thus far 42 consecutive patients with advanced PD (28 male, mean age: 63.3±7.2 yrs, mean duration of disease: 10.6±4.7 yrs, median Hoehn &Yahr stage: 2.5) have completed 24 MFU. STN-DBS significantly improved all scores (repeated measures ANOVA, all p=0.035). Post-hoc analyses showed a significant improvement from baseline to 6MFU (Wilcoxon signed rank-test, respectively paired t-test when criteria were fulfilled; all p=0.015) followed by a deterioration from 6MFU to 24MFU (motor examination n.s., all other p=0.041). Long-term outcomes comparing baseline to 24 MFU improved significantly for Scopa-motor examination and complications (all p=0.025), but not for PDQ-8, NMSQ and SCOPA-ADL.

Conclusions: This study provides evidence that bilateral STN-DBS has beneficial effects on QoL, non-motor and motor symptoms in patients with PD. The deterioration of all scales from 6MFU to 24MFU may have a variety of causes, e.g. disease progression. This effect was more pronounced on QoL, NMS and ADL which at 24MFU reached levels comparable to preoperative baseline while a significant improvement of motor symptoms was
sustained over two years. Long-term effects of DBS on specific NMS domains such as mood, sleep, and autonomic symptoms are now being studied.

SG 07
Clinical correlates of severe somnolence in Parkinson’s disease: results from an international naturalistic non-motor symptoms cohort

R. Taddei, A. Sauerbier, M. Qamar, K. Ray Chaudhuri (London, United Kingdom)

Objective: To compare patients with mild and severe daytime somnolence using cut-off values from item 15 of the Parkinson’s disease (PD) sleep scale (PDSS).

Background: Although risk factors for sudden onset of sleep (SoS) and somnolence in PD have been studied, large scale data is missing.

Methods: We classified 658 patients with PD into 3 subgroups based on PDSS item 15 scores, mild (>7) moderate (5-7) and severe (<5).

Results: Severe sleepiness was present in 38.8% (N=255). Compared to patients with mild sleepiness (N=360), those patients were of older age (mean in years 68.5±10.15 versus 64.8±11.4), had a longer disease duration (mean in years 5.8±5.1 versus 4.9±5), higher Hoehn and Yahr state (median 3 (1-5) versus 2 (0-5)), higher non motor symptoms (NMS) scale total score (63±41.6 versus 39.1±31.3), higher rate of hallucinations on NMS scale (0.8±1.8 versus 0.2±0.9), more autonomic dysfunction on NMS scale (16.8±12.7 versus 10.8±9.9), higher clinical impression of severity index cognition (1±1.1 versus 0.4±0.7), higher hospital anxiety and depression scale (13.4 ±8 versus 9.8±6.3) and poorer quality of life (mean PDQ-8 total score 10.25±6.5 versus 6.6±5.5). 75.7% of patients with severe sleepiness were treated with levodopa compared to 58.6 % with mild sleepiness (figure 1). Several patients had sudden onset of sleep.

Conclusions: Severe somnolence likely reflects a specific subtype (Park sleep) of PD (1). There is sensitivity to dopaminergic drugs and a higher NMS burden. These observations have clinical implications regarding personalised medication strategies in this subgroup.
SG 08  
Vmat2 heterozygote mice display motor dysfunction and progressive depressive-like behaviors

K. Ma, J. Huang, L. Liu, C. Han, X. Guo, S. Guo, L. Wang, Y. Shen, Y. Xia, F. Wan, N. Xiong, T. Wang (Wuhan, People’s Republic of China)

Objective: To assess motor and depressive behaviors in mice that are heterozygous for VMAT2 (VMAT2 HT).

Background: Dopamine (DA) is compartmentalized by the vesicular monoamine transporter 2 (VMAT2; SLC18A2), located in the plasma and vesicular membranes of dopaminergic neurons, which regulate levels of DA in neuronal compartments. Previous studies indicated that mice with a 50% genetic reduction in VMAT2 HT displayed depressive phenotype while performed normal locomotor activity tests at the time of 24 months.

Methods: Vmat2 HT mice were provided by professor Uhl Gr and bred from heterozygote-heterozygote crosses of KO mice. Genotypes were confirmed by PCR. Vmat2 HT and WT littermates of 16 months old and 30 months old were assessed of motor function and depressive behaviors respectively. Locomotor activity was assessed as total distance moved in the open field test and total time consumed in pole test. Tail suspension test and sucrose preference test were conducted to observe depressive behaviors.

Results: At the time of 16 months old, total distance moved in the open field test and total time consumed in pole test were similar between WT littermates and VMAT2 HT groups. VMAT2 HT mice (123.1±17.57s) display significant increase in immobility times in tail suspension test (p<0.05) and sucrose consume (54.73±3.911%) were significantly decreased in Vmat2 HT mice (p<0.05). At the time of 30 months old, both the results of open filed test and total time consumed in pole test suggested that Vmat2 HT mice displayed motor dysfunction compared with WT littermates (p<0.05). As for depressive-like behaviors, immobility time in tail suspension test of VMAT2 HT mice was significantly increased and sucrose consume in VMAT2 HT mice (40.92±7.655%) groups was significantly decreased (p<0.05).

Conclusions: Our data demonstrated that VMAT2 HT mice didn’t display motor dysfunction until 30 months old while depressive-like behaviors seemed to progress since 16 months old.

SG 09  
Which clinical features predict progressive supranuclear palsy pathology? A clinicopathological study on 437 autopsy cases and a literature review


Objective: To identify clinical features and investigations which predict PSP pathology during lifetime in the largest pathology PSP cohort reported to date compared to autopsy cases with relevant differential diagnoses.

Background: Progressive supranuclear palsy (PSP) is a neuropathologically defined disease entity. Current criteria for the clinical diagnosis of PSP are not sensitive in the early disease stages for manifestations other than Richardson’s syndrome. However, early diagnosis is important, particularly for the development of disease-modifying therapies.

Methods: We performed a systematic review of the literature published since 1996 to identify clinical features and investigations that may predict PSP pathology. We then extracted standardized data from clinical charts of patients with pathologically diagnosed PSP, as well as relevant disease controls, and calculated sensitivity, specificity and positive predictive value of key clinical features for PSP in this cohort.

Results: Of N=4166 identified articles identified by an automated database inquiry, N=254 met the predefined standards. The literature review identified clinical features predictive for PSP, including features of the four functional domains “ocular motor dysfunction”, “postural instability”, “akinesia”, and “cognitive dysfunction”. However, no biomarker or genetic findings were confirmed to predict PSP. No biomarker or genetic findings were
found reliable to predict definite PSP. High-quality original natural history data was available from patients with pathologically diagnosed PSP (N=206), CBD (N=54), MSA-P (N=51), PD (N=53), and FTLD (N=73). We identified clinical features of differential sensitivity and specificity that predict PSP pathology, including phenotypes other than PSP-RS.

**Conclusions:** The evidence from this extensive literature review and autopsy cohort presents a valuable basis for the revision of the diagnostic criteria for PSP.

**SG 10**
**Randomize study of occurrence of Parkinson’s syndrome in patients with rheumatoid arthritis**

*M. Mavlanov, S. Aslanova, G. Rakhimbaeva (Tashkent, Uzbekistan)*

**Objective:** We aimed to study an occurrence of Parkinson’s syndrome (PS), its relationship with duration of disease and age of patients with rheumatoid arthritis.

**Background:** Rheumatoid arthritis (RA) is a severe systemic disease which leads besides of points and organs to the defeat of central nervous system.

**Methods:** The clinical research was carried out in the department of rheumatology of the first clinic of Tashkent Medical Academy. We did neurologic exam in 80 patients with RA and did MRI angiography patients with PS. They aged 18-65 years (mean age 47 ± 1.6 years), of them 36 women and 14 men, 71.1% and 28.9% respectively. We eliminated patients with inherited Parkinson’s disease.

**Results:** Patients aged 40-60 years were the most common of all patients we studied. The duration of the disease lasts from 1.5 months to 27 years. The average duration of the disease is 10.5 years. In neurologic exam we found muscular rigidity in hands, aminia of face, absence of synkinetic reactions and finger tremor. We detected in 19 (23.75%) patients rigidity form and in 5 (6.25%) patients tremor form of PS. In MRI scan of all patients with PS we found the many rheumatoid vasculitis of subcortical nucleus vessels.

**Conclusions:** We concluded that PS is occurs in patients with RA to 20-25% more often, than its occurrence in all population. Rigidity form of PS amounts 79%. The severity of PS is higher than the RA is longer and the age of the patients greater.

**SG 11**
**An evaluation of the diagnostic utility of radiological biomarkers in PSP**


**Objective:** To critically evaluate the degree to which structural and molecular radiologic metrics fulfill criteria for diagnostic biomarkers of progressive supranuclear palsy (PSP).

**Background:** PSP is a pathologically defined neurodegenerative tauopathy with a variety of clinical presentations including Richardson’s syndrome (PSP-RS) and other variant PSP syndromes (vPSP). A large body of neuroimaging research has been conducted over the past two decades, with different structural MRI and molecular PET/SPECT biomarkers proposed for PSP. However, it is unclear whether there is enough evidence to support the inclusion of any of these biomarkers in clinical diagnostic criteria for PSP.

**Methods:** We queried the PubMed, Cochrane, Medline, and PSYCInfo databases for original research articles using postmortem or NINDS-SPSP criteria as the diagnostic standard from 1996-2016. Articles were subjected to methodological analysis using the Scottish Intercollegiate Guidelines Network checklist and independent experts collated standardized information on study design, patient characteristics, imaging metric, findings, and diagnostic
value for included articles. We defined a 5-level theoretical construct for the utility of neuroimaging biomarkers: 1=group-level findings, 2=biomarkers with demonstrable individual-level diagnostic utility, 3=biomarkers for early disease, 4=surrogate biomarkers of PSP pathology, and 5=definitive biomarkers of PSP pathology.

**Results:** The literature search identified 1737 abstracts, of which 193 articles met inclusion criteria and underwent review. Neuroimaging metrics that fulfilled criteria for level 2 biomarkers of PSP-RS included MRI midbrain measurements, frontal hypometabolism on FDG-PET, superior cerebellar peduncle measurements on diffusion MRI, striatal dopamine imaging and [18F]AV-1451 tau PET measurements. Midbrain measurements and frontal hypometabolism may provide level 3 biomarkers. No neuroimaging metric fulfilled criteria for level 4 or 5 biomarkers.

**Conclusions:** Data so far only supports neuroimaging biomarkers as level 2, or possibly level 3, biomarkers for PSP-RS. More work is needed to assess the value of these metrics in vPSP and in autopsy-confirmed cases to determine whether they could be useful level 4 biomarkers. Tau-PET imaging is promising but more work is needed to understand the biological underpinnings of the tau-PET signal in PSP.

**SG 12**
**Movement Disorder Society - Clinical Diagnostic Criteria for Progressive Supranuclear Palsy**


**Objective:** The International Parkinson and Movement Disorders Society-endorsed PSP Study Group aimed to provide an evidence- and consensus-based revision of the clinical diagnostic criteria for PSP.

**Background:** Progressive supranuclear palsy (PSP) is a neuropathologically defined disease entity. The NINDS-SPSP clinical diagnostic criteria, published in 1996, have excellent specificity, but their sensitivity is limited for variant PSP syndromes (vPSP) with presentations other than Richardson’s syndrome.

**Methods:** We searched the PubMed, Cochrane, Medline, and PSYCInfo databases for articles published in English since 1996, using postmortem diagnosis or the NINDS-SPSP criteria as the diagnostic standard. Secondly, we generated retrospective standardized clinical data from patients with autopsy-confirmed PSP, CBD, MSA-P, PD and FTLD-bvFTD. On this basis, diagnostic criteria were drafted, optimized in two modified Delphi evaluations, submitted to structured discussions with consensus procedures during a two-day meeting, and refined in three further Delphi rounds.

**Results:** Defined clinical, imaging, laboratory, and genetic findings serve as mandatory basic features, mandatory exclusion criteria or context-dependent exclusion criteria. We identified four functional domains (ocular motor dysfunction, postural instability, akinesia, cognitive dysfunction) as clinical predictors of PSP. Within each of these domains, we propose three clinical features that contribute different levels of diagnostic certainty. Specific combinations of these features define the diagnostic criteria, stratified by three degrees of diagnostic certainty (probable PSP, possible PSP, suggestive of PSP). Clinical clues and imaging findings represent supportive features.

**Conclusions:** Here, we present new criteria for the early, sensitive and specific clinical diagnosis of PSP on the basis of currently available evidence.

**SG 13**
**Parkinsonism revealing cerebral hematoma with moya moya disease**

Z. Brahem, I. Bedoui, A. Riahi, M. Mansour, J. Zaouali, R. Mrissa (Tunis, Tunisia)

**Objective:** The aim of this study is to describe a rare cause of parkinsonism.
**Background:** Moyamoya disease (MMD), a rare chronic, progressive cerebrovascular disease leads to occlusion of intracranial internal carotid arteries and its proximal branches. Movement disorders, as for parkinsonism, are rarely revealing this pathology.

**Methods:** We report a case of a 51-year-old female, who presented a tremor localized in her left arm.

**Results:** Clinical examination showed unilateral extrapyramidal syndrome. In the CT scan, we found a thalamic hematoma and intraventricular hemorrhage. She was diagnosed MMD based on the angiography demonstrating bilateral intracranial internal carotid artery stenosis with puff of smoke appearance. She did not consent for revascularization procedure and she had only medical treatment.

**Conclusions:** MMD is commonly associated with cerebral hemorrhages in adults. Intracerebral hematoma is the most frequently in the basal ganglia region. Thalamic bleed is relatively uncommon and found in about 21.4% patients. Clinical manifestations are usually hemiparesis. Movement disorders and especially parkinsonism as revealing symptom are very rare. To our knowledge only 8 patients had movement disorder in this context due to anatomical or functional lesions in basal ganglia. Movement disorders are rarely associated with hemorrhagic stroke as well as with MMD. In front parkinsonism, angio-MRI is mandatory to not misdiagnose this disease.

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**SG 14**

**Exposure to bifenthrin contributes to Parkinson’s disease in mouse model**

*C. Han, S. Liu, J. Huang, L. Liu, K. Ma, X. Guo, S. Guo, L. Wang, Y. Shen, Y. Xia, F. Wan, N. Xiong, T. Wang*  
(Wuhan, People’s Republic of China)

**Objective:** To explore the relationship between pyrethroid bifenthrin and Parkinson’s disease on mouse model.

**Background:** Pyrethroid is now widely used on account of its high efficiency and low toxicity compared to other pesticides. Bifenthrin, one pyrethroid used extensively, was previously demonstrated to cause developmental toxicity. Considering that some pyrethroid was demonstrated to induce dopaminergic degeneration, while the evidence for bifenthrin is still limited.

**Methods:** Mice were randomly divided into five groups (n=9, per group): vehicle group, 5 mg/kg bifenthrin group, 10 mg/kg bifenthrin group, 20 mg/kg bifenthrin group and 40 mg/kg bifenthrin group. Behavior assessment including pole test and rotarod test were conducted. Detection of dopamine, dopac, homovanillic acid and 5-HT by high performance liquid chromatography were performed. Besides, measurement of malondialdehyde (MDA), superoxide dismutase (SOD) and glutathione (GSH) were also done. Pathologically, protein level of tyrosine hydroxylase (TH), a-synuclein and vasicular monoamine transporter 2 (VMAT2) were evaluated by western blotting and immunofluorescence or immunohistochemistry.

**Results:** In this study, we first demonstrated that high dose of bifenthrin was able to cause decreased body weight in mice and bradykinesia indicated by pole test and rotarod test. Pathologically, bifenthrin caused loss of TH and accumulation of a-synuclein. Furthermore, bifenthrin induced decreased expression of VMAT2. Additionally, bifenthrin caused increased oxidative index such as SOD and glutathione which might contribute to the pathological changes.

**Conclusions:** Our data showed that bifenthrin could induce pathological change resembling PD in mice, providing strong evidence that bifenthrin exposure could contribute to the pathogenesis of PD.
SG 15
Genetic knock-down of HDAC4 attenuates rotenone-induced abnormal expression of a-synuclein by affecting autophagic flux in SH-SY5Y Cells


Objective: To assess whether histone deacetylase 4 (HDAC4) is related to the abnormal expression of a-synuclein (a-syn) via the autophagy pathway.

Background: The overexpression and aggregation of a-syn play central roles in the pathogenesis of Parkinson’s disease (PD). Therefore, the clearance of a-syn is a feasible and promising therapeutics alternative for PD. Previous studies indicated that aberrant histone acetylation could inhibit the autophagy process, which influence the abnormal overexpression and aggregation of a-syn.

Methods: The shRNA of HDAC4 and vehicle were transfected into SH-SY5Y cells respectively, then the cells were treated with 1µmol rotenone for 48 hours. The protein levels of HDAC4, a-syn, LC3-?, p62 and beclin-1 were evaluated by Western blot.

Results: After exposure in rotenone, the SH-SY5Y cells showed an abnormal increase in the expression of a-syn. However, after knock-down of HDAC4, the abnormal expression of a-syn was reversed. Moreover, the protein levels of LC3-? and belcin-1 were increased, while the level of p62 was decreased.

Conclusions: Reduced expression of HDAC4 reverses the abnormal expression of a-syn via activation of autophagy. HDAC4 is related to rotenone-induced elevated level of a-syn.

SG 16
Effects of different intensity exercises on motor function of PD rats as well as the regulation of DA

X. Liu, P. Chen, D. Qiao, M. Wang (Beijing, People’s Republic of China)

Objective: This paper research the intervention effect of the different intensity treadmill exercise on motor function of Parkinson’s ’s diseases (PD) model rats, and explore the most suitable intensity treadmill exercise intervention for prevention and treatment of PD.

Background: Parkinson’s disease (PD) is the second most common progressive, irreversible neurodegenerative disorder in the World. Leads to difficulty with activities of daily living (ADLs) and decline in quality of life (QOL). Treatment options for PD are limited to pharmacologic management and surgery. Less invasive alternatives, such as exercise, have captured the attention of scientists and clinicians as possible adjunctive therapy.

Methods: Clean level male SD rats were randomly divided into Control group, PD group,PD+6Ex group,PD+11Ex group and PD+16Ex group. PD model rats were established by injection of 6-OHDA in right medial forebrain bundle single point. Control groups rats received same dose of saline. The exercise groups were intervened by 4 weeks of treadmill exercise at 24 hours after the surgery, the corresponding running speed of each group is 6m/min,11m/min and 16m/min,30 min/day,5day/week.

Results: Cylinder test showed that, the effect of the intervention became more and more obvious with the time prolonged. Grid test results showed, after 4 weeks exercise intervention, compared with PD group of rats, the slip times of PD+11Ex group significantly reduced. Immunohistochemical results showed that, compared with PD group, the expression of TH and D2DR in striatum of PD+11Ex group and PD+16Ex group rats increased significantly .The variation trend of the results of Western Blot was in accordance with the results of immunohistochemistry. The expression levels of TH and D2DR in striatum in low intensity exercise group rats have low correlations with the changes of motor ability ,but in medium intensity exercise group rats have high correlations with the changes of motor ability.
**Conclusions:** Four weeks treadmill exercise intervention can reduce movement dysfunction of PD model rats, and significantly increased TH and D2DR expression level in striatum. This suggests that DA systems involved in the regulation of motor function in rats; and the neurobiological mechanisms of exercise intervention reduced the motor dysfunction in PD model rats may related to the regulation effect of TH and D2DR.

**SG 17**

**Treatable rare movement disorders**


**Objective:** To classify therapies of RMD into enzyme replacement therapy, specific dietary changes, avoidance or management of certain triggers, and others.

**Background:** Rare diseases (RD) collectively are very common and encompass more than 7000 different disorders, but the number continues to grow every year. Movement disorders constitute the hallmark feature of several RD and a significant proportion of these disorders are amenable to treatment. Although effective symptomatic treatment are available for many rare movement disorders (RMD), some are amenable to pathogenesis-targeted therapeutic strategies.

**Methods:** Our study group performed a systematic literature review to identify treatable RMD for which evidence for effective treatment exists.

**Results:** We identified at least 33 treatable RMD affecting children and adults. Different targets for these treatable conditions include dietary intervention in 9/33 (i.e. abetalipoproteinemia); avoidance of triggers 8/33 (e.g. glutaric aciduria type 1), enzyme replacement or substrate reduction 2/33 (e.g. Gaucher disease, Niemann-Pick type C), vitamin supplementation 6/33 (e.g. biotinidase deficiency), dopamine replacement 6/33 (e.g. dopa-responsive disorders), copper depleting agents 2/33 (e.g., Wilson disease), replacement therapies 2/33 (e.g., chenodeoxycholic acid in cerebrotendinous xanthomatosis), *compensatory enzymatic activity* 1/33 (e.g. Aromatic amino acid decarboxylase deficiency) and ion channel modulation 2/33 (e.g. Episodic ataxia type 2).

**Conclusions:** Increased awareness of treatable RMD through a systematic approach may facilitate the use of specific treatments capable of preventing, improving, or reversing neurological damage associated with this group of movement disorders.
Objective: Investigate the antineural antibodies (ANAb) level in the individuals with Tourette syndrome (TS) and the relationship with clinical characteristics. Analyze the clinical results and safety of globus pallidus internus (GPi) deep brain stimulation (DBS) in refractory TS patients and the comparison of ANAb level of preoperation and postoperation.

Background: Autoimmune etiology associated with TS. DBS is an effective and safe treatment.

Methods: The level of serum ANAb was detected in 15 refractory TS patients and 4 of them were treated with GPi DBS. The patients were interviewed to evaluate the severity of their tics and others by YGTSS, YALE-BROWN and SDS at preoperative and 1 month, 6 months, 1 year and subsequent follow-up after the surgery. Side effects were documented. Comorbid neuropsychiatric disorders were also identified based on the information from the interviews with the patients.

Results: In the group of 15 TS patients the course of disease, YGTSS Motor scores and YGTSS total scores are positively associated with the age (P<0.05), YGTSS Motor scores and YGTSS total scores are positively associated with the course of disease (P<0.05). There is a lack of correlation between the ANAb level and the course of disease, gender and YGTSS scores (P>0.05). 4 refractory TS patients was performed GPi-DBS procedure. The time of follow-up is 60.00±21.91 months. Compare with the preoperation, there is a significant difference in YGTSS score from 6 months after Gpi-DBS. There is a lack of correlation between the ANAb level and DBS treatment. None of the 4 patients showed serious permanent side effects.

Conclusions: This study indicates patients’ symptoms are more severe, the patients are older and the courses of disease are longer. There is no significant correlation between the ANAb level and the course of disease, gender and YGTSS scores which showed that autoimmune has no effect on the development of the disease. The results suggest GPi DBS is an effective and safe treatment for refractory TS patients. There is a reduction of ANAb level compared with preoperation and postoperation which indicated the mechanism of DBS may involve autoimmune reaction. But there is no significant difference because of the small sample size (only 2 cases). So this study needs to expand the sample size to further clarify the relationship.

SG 19
Non-motor symptoms in Parkinson’s disease and putamen dopamine transporter uptake (DaTscan) uptake: A survey of 85 patients

Objective: We addressed association between 30 non-motor symptoms (NMS) (using the validated Parkinson’s disease (PD) NMS Scale (NMSS)), and DaTscan putamen uptake ratios as part of a large-scale multicentre naturalistic NMS study.
**Background:** NMS in PD are heterogeneous and have been proposed to have both dopaminergic and non-dopaminergic pathophysiology. Pre-synaptic striatal dopamine transporter (DaTscan) may thus provide a surrogate marker for some dopaminergic NMS.

**Methods:** Data was collected from the UK arm of the NMS International Longitudinal Study (NILS, UKCRN No 10084), 85 PD patients who had undergone a battery of motor and non-motor assessments as well as DaTscan ($^{123}$I FP-CIT, Ioflupane) imaging were analysed. Association between NMS and DaTscan uptake was calculated using Spearman’s rank correlation.

**Results:** PD patients (71.8% male, mean age 62.05±12.05 years, mean disease duration 3.28±3.43 years, age of PD onset 58.77±12.27 years) had a mean NMSS total score of 50.35±40.62 and a mean NMS Questionnaire total score of 7.44±6.51. NMS and DaTscan putamen uptake correlation was statistically significant for visual hallucinations, delusions, dribbling of saliva, and olfaction (table 1). NMS burden and DaT uptake had a “very weak” correlation (right putamen $r=-0.191$, $p=0.080$; left putamen $r=-0.231$, $p=0.033$).

**Conclusions:** Although a minority of 30 NMS and NMS burden do correlate with striatal DaT scan uptake, the association if very weak and largely not significant. This suggests that the dominant pathophysiology of NMS is predominantly non-dopaminergic.

<table>
<thead>
<tr>
<th>Table 1: Association</th>
<th>Right Putamen</th>
<th>Left Putamen</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMS1 Orthostatic hypotension</td>
<td>0.147</td>
<td>0.098</td>
</tr>
<tr>
<td>NMS2 Blackout</td>
<td>-0.209</td>
<td>-0.202</td>
</tr>
<tr>
<td>NMS3 Daytime sleepiness</td>
<td>-0.073</td>
<td>-0.147</td>
</tr>
<tr>
<td>NMS4 Fatigue</td>
<td>-0.147</td>
<td>-0.146</td>
</tr>
<tr>
<td>NMS5 Difficulty sleeping</td>
<td>0.204</td>
<td>0.044</td>
</tr>
<tr>
<td>NMS6 Restless legs</td>
<td>-0.016</td>
<td>-0.143</td>
</tr>
<tr>
<td>NMS7 Loss of interest</td>
<td>-0.131</td>
<td>-0.101</td>
</tr>
<tr>
<td>NMS8 Lack motivation</td>
<td>-0.201</td>
<td>-0.181</td>
</tr>
<tr>
<td>NMS9 Nervous</td>
<td>-0.080</td>
<td>-0.024</td>
</tr>
<tr>
<td>NMS10 Depressed</td>
<td>-0.006</td>
<td>0.089</td>
</tr>
<tr>
<td>NMS11 Flat moods</td>
<td>-0.051</td>
<td>-0.143</td>
</tr>
<tr>
<td>NMS12 Pleasure problems</td>
<td>-0.035</td>
<td>0.029</td>
</tr>
<tr>
<td>NMS13 Visual hallucinations</td>
<td>-0.238</td>
<td>-0.287</td>
</tr>
<tr>
<td>NMS14 Delusions</td>
<td>-0.230</td>
<td>-0.203</td>
</tr>
<tr>
<td>NMS16 Double vision</td>
<td>-0.022</td>
<td>-0.137</td>
</tr>
<tr>
<td>NMS16 Concentration problems</td>
<td>-0.108</td>
<td>-0.167</td>
</tr>
<tr>
<td>NMS17 Short-term memory problems</td>
<td>-0.011</td>
<td>-0.111</td>
</tr>
<tr>
<td>NMS18 Memory problems</td>
<td>-0.042</td>
<td>-0.058</td>
</tr>
<tr>
<td>NMS19 Dribbling of saliva</td>
<td>-0.264</td>
<td>-0.253</td>
</tr>
<tr>
<td>NMS20 Swallowing difficulty</td>
<td>-0.119</td>
<td>-0.161</td>
</tr>
<tr>
<td>NMS21 Constipation</td>
<td>-0.138</td>
<td>-0.202</td>
</tr>
<tr>
<td>NMS22 Urinary urgency</td>
<td>-0.099</td>
<td>-0.156</td>
</tr>
<tr>
<td>NMS23 Urinary frequency</td>
<td>-0.044</td>
<td>-0.036</td>
</tr>
<tr>
<td>NMS24 Nocturia</td>
<td>-0.018</td>
<td>-0.056</td>
</tr>
<tr>
<td>NMS25 Altered sex interest</td>
<td>0.082</td>
<td>-0.032</td>
</tr>
<tr>
<td>NMS26 Problems having sex</td>
<td>-0.056</td>
<td>-0.023</td>
</tr>
<tr>
<td>NMS27 Pain</td>
<td>0.023</td>
<td>0.007</td>
</tr>
<tr>
<td>NMS28 Olfactory changes</td>
<td>-0.362</td>
<td>-0.151</td>
</tr>
<tr>
<td>NMS29 Weight change</td>
<td>-0.102</td>
<td>-0.049</td>
</tr>
<tr>
<td>NMS30 Excessive sweating</td>
<td>-0.127</td>
<td>-0.122</td>
</tr>
<tr>
<td>NMSS Total</td>
<td>-0.154</td>
<td>-0.213</td>
</tr>
</tbody>
</table>
Mild cognitive impairment according to MDS PD-MCI level I criteria as a risk factor for Parkinson’s disease dementia – a validation study

Jeroen Hoogland MD1 *, Judith A. Boel MSc1,2, Rob M.A. de Bie MD PhD1, Ben A. Schmand PhD2,3, John C. Dalrymple-Alford PhD4, Connie Marras MD PhD5, Charles H. Adler MD PhD6, Daniel Weintraub MD7, Carmen Junque PhD8, Kenn F. Pedersen PhD9, Brit Mollenhauer MD10, Jennifer G. Goldman MD PhD11, Alexander I. Tröster PhD12, David J. Burn MD PhD13, Irene Litvan MD PhD14 and Gert J. Geurtsen PhD3 on behalf of the MDS Study Group “Validation of Mild Cognitive Impairment in Parkinson Disease”

1 Department of Neurology, Academic Medical Center Amsterdam, The Netherlands
2 Department of Psychology, University of Amsterdam, The Netherlands
3 Department of Medical Psychology, Academic Medical Center Amsterdam, The Netherlands
4 New Zealand Brain Research Institute, Brain Research New Zealand - Centre of Research Excellence, Christchurch, New Zealand
5 Morton and Gloria Shulman Movement Disorders Centre and the Edmond J Safra Program in Parkinson’s disease, Toronto Western Hospital, University of Toronto, Canada
6 Arizona Parkinson’s Disease Consortium, Mayo Clinic Arizona, Scottsdale, Arizona, USA and Banner Sun Health Research Institute, Sun City, Arizona, USA
7 Departments of Psychiatry and Neurology, University of Pennsylvania School of Medicine, and Parkinson’s Disease and Mental Illness Research, Philadelphia Veterans Affairs Medical Center, Philadelphia, PA, USA
8 Department of Psychiatry and Clinical Psychobiology, Faculty of Medicine, University of Barcelona, Spain
9 The Norwegian Centre for Movement Disorders, Department of Neurology, and Memory Clinic, Stavanger University Hospital, Stavanger, Norway
10 Paracelsus-Elena-Klinik, Kassel, Germany, and University Medical Center Goettingen, Department of Neurosurgery and Institute of Neuropathology, Goettingen, Germany
11 Department of Neurological Sciences, Section of Parkinson Disease and Movement Disorders, Rush University Medical Center, Chicago, USA
12 Department of Clinical Neuropsychology and Center for Neuromodulation, Barrow Neurological Institute, Phoenix, Arizona, USA
13 Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK
14 Department of Neurosciences University of California San Diego, Movement Disorder Center, San Diego, California

* These authors contributed equally

Objective: The main aim of this international study was to evaluate the predictive validity of the abbreviated (Level I) PD-MCI criteria by assessing their contribution to the hazard of PD dementia (PDD).

Background: The abbreviated The International Parkinson and Movement Disorder Society criteria for mild cognitive impairment in Parkinson’s disease (PD-MCI) need validation.

Methods: Individual patient data were available from eight studies on PD cognition that provided information on demographics, motor examination, depression, neuropsychological examination suitable for application of Level I PD-MCI criteria, and longitudinal follow-up for conversion to dementia. Level I criteria were rated using one neuropsychological test per each of five cognitive domains and according to three cut-offs: -1, -1.5 and -2SD. Survival analysis evaluated the predictive value of Level I criteria for future cognitive decline as expressed by the relative hazard of PDD.

Results: 1045 patients were included. Level I PD-MCI criteria, age, and severity of PD motor symptoms independently increased the hazard of PDD. There was a trend of increasing hazard of dementia for those fulfilling successively lower cut-offs on neuropsychological assessment.
Conclusions: PD-MCI classification according to Level I criteria confers an independent contribution to the hazard of PD dementia. This finding supports the predictive validity of the abbreviated PD-MCI criteria and suggest their utility in longitudinal research, which is important given practical considerations when choosing a neuropsychological test battery.

Motor and non-motor biomarkers in de novo Parkinson’s disease: preliminary data from the Kassel-Kings-Madrid cohort study

K Ray Chaudhuri (1), Brit Mollenhauer (2), Pablo Martinez-Martin (3), Carmen Rodriguez-Blazquez (3), Anna Sauerbier (1), Alexandra Rizos (1), Claudia Trenkwalder (4)

1 King's College Hospital and King's College, London, United Kingdom
2 Paracelsus-Elena Hospital, Center of Parkinsonism and Movement Disorders, Kassel, Germany
3 National Center of Epidemiology and CIBERNED, Carlos III Institute of Health, Madrid, Spain
4 University Medical Center Goettingen, Goettingen, Germany; Paracelsus-Elena Hospital, Center of Parkinsonism and Movement Disorders, Kassel, Germany
London, United Kingdom
London, United Kingdom

Objective: Combining two cohort studies led by London, UK (the NILS cohort) and Kassel, Germany (DeNoPa cohort) with independent data analysis in Madrid allows an unique holistic motor and non-motor biomarkers evaluation in a large de novo Parkinson's disease (DNPD) cohort.

Background: Non-motor symptoms (NMS) are important to support the clinical diagnosis of Parkinson's disease (PD) and to identify its prodromal premotor state. Systematic and multimodal data capture of NMS in PD is uncommon even in well established longitudinal cohort studies. Most studies have extensive motor assessments and minimal NMS assessments, usually olfactory and cognitive testing.

Methods: Cross sectional and longitudinal (24 months) multicenter data from DNPD using a range of PD stage (Hoehn and Yahr), motor function (UPDRS III), NMS scales (NMS Scale (NMSS), Mini Mental Status Examination (MMSE)), quality of life (PDQ-39) and other optional imaging/laboratory biomarkers.

Results: 240 nondemented DNPD cases have been evaluated (66.3% males, age 65.7±10.2 years). Key data suggest that between baseline (de novo) and 24 months follow-up there is significant worsening of motor scores (p<0.001), NMS burden and NMSS total score (p=0.017) and cognitive abilities (by MMSE)(p=0.001) while quality of life (PDQ-8) was not clinically significant changed (p=0.104). These changes showed negligible or weak association (range: 0.003 to 0.263) with age, PD duration and Hoehn and Yahr stage at baseline. Despite of the global worsening of NMSS scores, mood/apathy and sexual dysfunction scores remained unaltered at follow up.

Conclusions: NMS reveal progression in the first 24 months after diagnosis in PD and could support endpoints of putative neuroprotective clinical trials.
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1185 A randomized, double-blind, placebo-controlled study of the D1 receptor antagonist ecopipam for children and adolescents with Tourette syndrome
D. Gilbert, T. Murphy, J. Jankovic, C. Budman, K. Black, R. Kurlan, K. Coffman, J. McCracken, J. Juncos, J. Grant, R. Chipkin (Cincinnati, OH, USA)

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1341 Subthalamic Nucleus Deep Brain Stimulation in Early Stage Parkinson’s Disease Reduces the Risk of Polypharmacy: Five-Year Analysis

1371 Deep Brain Stimulation in Parkinson’s disease: Outcome after more than nine years
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