MDS-ES Parkinson's Disease Summit: Therapeutic Milestones in Parkinson's Disease

International Parkinson and Movement Disorder Society European Section

MARCH 18-20, 2020

VENICE, ITALY

LATE-BREAKING ABSTRACTS

LBA 1

Health Care Provision and Health Related Quality of Life in Late Stage Parkinson's Disease

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Objective: To describe and assess factors associated with health related quality of life (HRQoL) in patients with late stage Parkinson's disease (PD), with a special focus on health care factors.

Background: In the late and most severe stage of PD, both motor and non-motor symptoms (NMS) are pronounced and the patients become dependent on help in activities of daily living (ADL). Consequently, there is an increasing demand on health and social care resources. Increased knowledge on factors associated with HRQoL in late stage PD could serve as an important base for optimizing health and social care for these severely afflicted patients.

Methods: The Care of Late Stage Parkinsonism (CLaSP) project is the so far largest study on late stage PD, defined as Hoehn and Yahr stages IV and V in "on" and/or having a substantial need of help with ADL; Schwab and England ≤ 50%. Participants were recruited from six European countries (the UK, Germany, the Netherlands, Portugal, France and Sweden), at leading movement disorder clinics, with the goal to establish a large cohort of patients. Baseline data include 692 patients and their 470 informal caregivers. HRQoL was assessed with the PDQ-8 and the DEMQoL-Proxy in patients with dementia (MMSE < 18). A study specific resource utilization questionnaire was used to determine the use of health care resources. Factors potentially associated with HRQoL were assessed and (for the PDQ-8) entered into multivariable linear regression analyses. The analyses were controlled for age, gender, disease duration and disease severity.

Results: The median age was 77 years; the median disease duration was 14 years; 54% were male. The majority had a partner (66%); 72% lived in ordinary housing and 28% in a nursing home. The median UPDRS III score was 47; the median NMSS score was 102; the median MMSE score was 24 and the median GDS-15 score was 6. In the simple linear regression analyses, HRQoL was positively associated with independence in ADL, better motor function, fewer NMS, better cognition, less depressive symptoms and having been in contact with a PD-nurse during the past 3 months. For patients with dementia; having a partner and hospital admittance during the past 3 months were positively associated with HRQoL. The multivariable analyses identified better motor function, fewer NMS and less depressive symptoms as positively associated with HRQoL.

Conclusions: The results indicate that optimizing treatment for motor and NMS, including depressive symptoms, could improve HRQoL for late stage PD patients. PD specific health care resources are likely important in providing this.

LBA 2

New compound increasing glucocerebrosidase activity on primary cell cultures obtained from patients with GBA-associated Parkinson's disease

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Objective: To determine whether new chemical modifications of the previously described allosteric GCase chaperone NCGC00241607 (Aflaki E et.al Neurosc. 2016) increase GCase activity in monocyte-derived macrophages from GBA-PD patients.

Background: Mutations in the glucocerebrosidase gene (GBA) are the most common cause of Parkinson disease (PD). GBA encodes the lysosomal enzyme glucocerebrosidase (GCase). The mechanisms by which loss of GCase activity due to GBA mutations contributes to PD remain unclear. Therefore, there is no therapy for PD associated with mutations in the GBA gene (GBA-PD). Last data showed that small molecule chaperones as ambroxol or isofagomine (IFG) could cross the blood brain barrier and help mutant GCase refold and traffic correctly to lysosomes. However, both compounds bind to GCase active site. Allosteric GCase molecular chaperones could be more effective in restoring of GCase activity

Methods: Peripheral blood samples were collected from GBA-PD patients (mean age 59,1±4,0 5males) mutations (N370S, L444P). To evaluate the effect of isofagomine and new compounds on GCase activity, all compounds were added to cell cultures on day 4 to the final concentrations of 50 μM (IFG) and 4 μM (chemical modifications, including N2), and the cells were incubated for further 4 days. Macrophages were differentiated from purified monocytes in standard conditions. GCase activity were measured by LC-MS/MS in dried spot of macrophages (2x10^6 cells/ml).

Results: We showed an increase GCase activity in macrophages from GBA-PD patients after treatment with pharmacological chaperone (IFG (47,23 (10,29-216,78)) compared to macrophages from GBA-PD patients without treatment (17,71 (4,20-27,67)) p

Conclusions: We showed an increase GCase activity in macrophages from GBA-PD patients treated with IFG and N2 compound. It is interesting to note that the effectiveness of restoring the GCase activity strongly depended on the type of GBA mutations. In the case of N370S the effectiveness in restoration of GCase activity was compatible with well-known GCase molecular chaperone IFG. Our results suggest that new potential allosteric GCase chaperone might be effective in restoration of GCase activity.
The study was supported by RSF № 17-75-20159

Table 1. GCase activity in patients with Parkinson's disease associated with mutation in the *GBA* gene.

Patients	GBA mutation	GCase activity, mM/l/h		
		0	+ IFG, 50 μM	+ N2, 4 μM
GBA-PD 1	N370S	12,54	43,41	35,54
GBA-PD 2	N370S	23,92	156,81	-
GBA-PD 3	L444P	8,3	146,65	-
GBA-PD 4	L444P	21,67	180,74	14,82
GBA-PD 5	N370S	24,28	46,57	-
GBA-PD 6	L444P	16,46	42,42	15,96
GBA-PD 10	L444P	15,16	10,29	-
GBA-PD 13	N370S	18,92	120,11	117,68

LBA 3

Does the Degree of Trunk Bending Predict Patient Disability, Motor Impairment, Falls, and Back Pain in Parkinson's Disease?

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Objective: (1) To explore the association between the degree of postural abnormalities, functional deficits and disability in a large cohort of PD patients with PA and (2) to identify cut-off values of trunk bending for limitations in activities of daily living (ADLs), motor impairment, falls, and back pain.

Background: Postural abnormalities (PA) in Parkinson's disease (PD) are a spectrum of trunk misalignment, ranging from a "typical" parkinsonian stooped posture to progressively more significant degrees of spine deviation in the sagittal, frontal or coronal planes. So far, no studies have explored the association between the severity of PA and functional deficits and disability. Similarly, no cut-off values have been provided in the literature to identify a specific cluster of PD patients with PA at risk of developing more severe motor impairments and disability related to the PA severity.

Methods: 283 PD patients with at least 5° of forward trunk bending (FTB), lateral trunk bending (LTB) or forward neck bending (FNB) have been enrolled. The degree of PA was calculated using a wall goniometer (WG) and software-based measurements (SBM). Limitation in ADLs was assessed by the Movement Disorders Society Unified PD Rating Scale [MDS-UPDRS] part II. Values above or equal to 17 identified moderate/severe limitation. Motor impairment was assessed using the MDS-UPDRS part III. Values above or equal to 33 identified moderate/severe motor impairments. A history of falls was defined by at least one fall in the previous month. The presence of pain was defined as at least 4 out of 10 at the Numeric Rating Scale. Logistic regression models were used to identify the relationship between the degree of bending (independent variable) and the limitation in ADLs, motor impairment, falls, and back pain (dependent variables). The optimal cut-off values were identified using receiver operating characteristic (ROC) curves.

Results: Significant associations between modified Hoehn & Yahr stage, disease duration, and sex and limitation in ADLs, motor impairment, back pain intensity, and history of falls have been reported. Degree of trunk bending was associated only with motor impairment in LTB (odds ratio [OR] 1.12; 95% confidence interval [CI], 1.03-1.22). ROC curves showed that patients with LTB of 10.5° (SBM, AUC 0.626) might have moderate/severe motor impairment.

Conclusions: For the first time the association between the severity of PA and functional deficits and disability has been explored. The severity of PA does not fully explain limitation in ADLs, motor impairment, falls, and back pain. Multiple factors possibly related to an aggressive PD phenotype may account for disability in PD patients with FTB, LTB, and FNB.