Evidence of UPR activation in both AD and PD suggests that the neurons are subjected to ER stress, but no studies have investigated the UPR in patients who have dementia with PD and AD pathology. The aim of this study, presented by Jean-Ha Baek, PhD, Karolinska Institute, Huddinge, Sweden, was to investigate changes in the UPR pathway in deceased subjects with PD with dementia (PDD) and dementia with Lewy bodies (DLB) in comparison with patients with AD and control subjects.

Postmortem brain tissue from 4 brain regions was provided by Brains for Dementia Research, United Kingdom, for evaluation (Table 1).

Table 1. Number and Type of Brain Tissue Samples

	Number of Cases			
Brain Region	AD	DLB	PDD	Control
Prefrontal cortex (BA 9)	11	44	28	16
Temporal cortex (BA 21)	0	35	33	25
Cingulate gyrus (BA 24)	16	40	10	23
Parietal cortex (BA 40)	15	47	33	23

AD=Alzheimer's disease; BA=Brodmann area; DLB=dementia with Lewy bodies; PDD=Parkinson's disease with dementia.

GRP78/BiP protein levels were quantified with western blot to measure the degree of UPR activation. Binding immunoglobulin protein (GRP78/BiP) expression patterns were assessed with immunohistochemistry.

Brain tissue from the cingulate gyrus of patients with PDD and those with DLB had a significant increase in the level of GRP78/BiP protein compared with tissue from patients with AD and control subjects (p=0.000 for all comparisons). GRP78/BiP protein expression in the parietal cortex was significantly decreased in brain tissue from patients with AD compared with control subjects (p=0.000) and significantly increased in tissue from patients with PDD compared with patients with AD (p=0.002) and in patients with DLB compared with those with AD (p=0.001). No significant differences were observed in GRP78/BiP levels in the prefrontal cortex and temporal cortex between any of the brain tissue sample groups.

Immunohistochemical studies detected GRP78/BiP protein in the cytoplasm of prefrontal cortex neurons in brain tissue from patients with AD, PDD, and DLB and controls. Although the labeling intensity was slightly increased in AD, PDD, and DLB patient samples compared with controls, the intensity was similar across the different disease groups.

This was the first study to investigate changes in the UPR pathway in deceased subjects with PDD and DLB in comparison with patients with AD and control subjects. Pearson correlation analysis found no association between changes in the GRP78/BiP protein level and Mini-Mental State Examination scores before death, rate of decline in Mini-Mental State Examination score, or global and regional pathologic scores for α-synuclein, plaques, and tangles. There was no correlation of Hoehn and Yahr scores with GRP78/BiP levels in a subset of subjects with PDD.

DBS Improves FOG in Patients With PD

Written by Toni Rizzo

High-frequency deep brain stimulation (DBS) is effective for relief of Parkinson's disease (PD) symptoms. However, studies on the effect of subthalamic nucleus DBS (STN-DBS) on freezing of gait (FOG) have reported inconsistent results, with some suggesting that STN-DBS alleviates FOG [Davis JT et al. *Clin Neurol Neurosurg* 2006] and others reporting worsening of gait and balance [van Neunen BFL et al. *Mov Disord* 2008; Krack P et al. *N Engl J Med* 2003].

The objective of the Vercise Implantable Stimulator for Treating Parkinson's Disease trial [VANTAGE; NCT01221948], presented by Michael T. Barbe, MD, University Hospital, Cologne, Germany, was to evaluate motor function improvement in patients with moderate to severe Parkinson's disease following treatment with bilateral STN-DBS. Prospective and nonrandomized, VANTAGE is open-label interventional trial in which a total of 40 patients underwent STN-DBS. DBS was delivered with the new Vercise DBS System, a multiple-source, eight-contact, constant-current system that is implantable and rechargeable.

FOG was assessed before and after surgery with Unified Parkinson's Disease Rating Scale (UPDRS) II Item 14, the Freezing of Gait Questionnaire (FOGQ), and a videotaped walk test known to provoke FOG (with and without dual tasks). For the postsurgery tests, FOGQ was given at 26 weeks and the walking test at 12, 26, and 52 weeks after implantation. The patients were also assessed with the Core Assessment Program for Surgical Interventional Therapies motor tests, Tremor Rating Scale, Dyskinesia Rating Scale, Parkinson's Disease Questionnaire 39, Short Form 36 Health Survey, and the Schwab and England Activities of Daily Living Scale. Resource utilization was assessed and patient motor diaries collected over 3 days at all subsequent visits.

The cohort was 67.5% male and 32.5% female, with a mean age of 60.2 years. At baseline, 26 of the 38 patients

(68%) had FOG. Duration of Parkinson's disease symptoms was 12.6 years in patients with FOG and 9.3 years in those without FOG. The total UPDRS, UPDRS III–meds off, and UPDRS III–meds on scores were similar between patients with and without FOG at baseline. At baseline, the L-dopa equivalent daily dose was 1305.0 mg in the group with FOG and 1653.6 mg in the group without.

At 26 weeks after surgery, the mean total FOGQ score was reduced by >50%. STN-DBS lowered the number of patients with FOG, as defined by FOGQ Item 4, from 26 of 38 patients at baseline to 13 of 38 patients at 26 weeks. The occurrence of FOG as measured with UPDRS II Item 14 declined over 52 weeks. UPDRS III Item 29 results showed that STN-DBS improved gait in this cohort over 52 weeks.

STN-DBS significantly reduced FOG and improved gait in this cohort of patients with Parkinson's disease. Further analysis of the videotaped walking tests might provide additional insights into the effects of STN-DBS on FOG, especially with respect to potential changes in different FOG subtypes and patterns.

Motor and Nonmotor Symptoms of PD Improve With Exercise

Written by Toni Rizzo

Exercise increases neuron proliferation in animal studies and improves motor function in patients with early-stage Parkinson's disease (PD). Multiple studies have demonstrated that the LSVT BIG® physical therapy exercise program is effective for improving the motor symptoms of PD. LSVT BIG is a program developed by LSVT Global that uses physical and occupational therapy in an intensive, whole-body, amplitude-based training protocol to treat individuals with PD. Khashayar Dashtipour, MD, PhD, Loma Linda University School of Medicine, Loma Linda, California, USA, presented the results of a pilot study comparing the effects of the LSVT BIG program with those of a one-on-one exercise program in patients with PD.

Nine patients with early- to middle-stage PD were randomly assigned to the LSVT BIG physical therapy exercise program (n=4) versus a one-on-one exercise program consisting of treadmill plus seated trunk and limb exercise (n=5). Both exercise programs took place in 16 1-hour supervised sessions. The goal was to compare the effects of each program on motor as well as on nonmotor symptoms in these patients with PD. The patients were assessed before and after the exercise intervention with the Unified Parkinson's Disease Rating Scale (UPDRS), UPDRS motor (UPDRS M), Beck Depression Inventory (BDI), Beck Anxiety Inventory, and Modified Fatigue Impact Scale (MFIS). The assessments were given at baseline (first evaluation) and monthly at 3 follow-up visits (second, third, and fourth evaluations). Follow-up data were compared with baseline data using Wilcoxon rank sum testing. The analysis was repeated separately for each of the assessments and for each evaluation period.

In the combined cohort of all 9 patients, all assessment results were improved from baseline at the follow-up evaluations, with statistically significant decreases in the UPDRS score at the second (p=0.0237), third (p=0.0361), and fourth (p=0.0142) evaluations. UPDRS M scores were significantly decreased from baseline at the third (p=0.0208) and fourth (p=0.0313) evaluations. BDI scores were significantly decreased at the second (p=0.0014), third (p<0.0001), and fourth (p<0.0001) evaluations. MFIS scores were significantly decreased only at the fourth evaluation (p=0.0022).

There were no significant differences between the LSVT BIG physical therapy and one-on-one exercise groups at any of the evaluations except for the MFIS score, which was significantly decreased from baseline to the fourth evaluation (–11.2 vs 0.0, p=0.0159) in the one-on-one exercise group compared with the LSVT BIG group. Changes from baseline to the fourth evaluation for the other assessments in the one-on-one exercise group compared with the LSVT BIG group are shown in Table 1.

Table 1. Change From Baseline to Fourth Evaluation, Both Groups

	One-on-One Exercise	LSVT BIG	p Value
UPDRS	–5.0	–8.3	0.4841
UPDRS M	–2.8	–6.8	0.2778
BDI	–2.0	–2.5	0.4524
BAI	–3.0	–0.5	0.2381
MFIS	–11.2	0.0	0.0159

BAI=Beck Anxiety Inventory; BDI=Beck Depression Inventory; MFIS=Modified Fatigue Impact Scale; UPDRS=Unified Parkinson's Disease Rating Scale; UPDRS M=Unified Parkinson's Disease Rating Scale motor.

The results of this pilot study demonstrated a positive effect of exercise and physical therapy on motor and nonmotor symptoms in patients with PD, with reductions in all scores from baseline. The only significant difference between the 2 groups was the significantly reduced MFIS score at the final evaluation in the one-on-one exercise group compared with the LSVT BIG group. The results of this pilot study suggest that one-on-one exercise could be at least as effective as the LSVT BIG physical therapy program for improving the symptoms of PD, but larger trials are needed to validate these data.