Parkinson's Disease Research Review™

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Issue 25 – 2016

In this issue:

Abbreviations used in this issue:

CSF = cerebrospinal fluid; **DBS** = deep-brain stimulation; **GPI** = globus pallidus pars interna; **PD** = Parkinson's disease; **PDQ** = Parkinson's Disease Questionnaire; **QOL** = quality of life **SPECT** = single-photon emission computed tomography; **STN** = subthalamic nucleus **UPDRS** = Unified Parkinson's Disease Rating Scale.

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Welcome to issue 25 of Parkinson's Disease Research Review.

Papers selected for this issue include a comparison of the GPI (globus pallidus pars interna) and STN (subthalamic nucleus) as targets for DBS (deep-brain stimulation) in patients with advanced PD. European researchers reported that the effects of post-STN-DBS apathy on health-related QOL could negate the benefits of treatment on motor function. Other included research identified pathogenic α-synuclein species in CSF exosomes obtained from patients with PD and dementia with Lewy bodies, which could trigger soluble α-synuclein oligomerisation in target cells and confer disease pathology. The final paper for this issue looked at the potential value of submandibular glands as a peripheral biopsy site for diagnosing early PD.

I hope you find this issue's selection useful in your everyday practice, and I look forward to receiving your questions and comments.

Kind Regards,

Dr Paul Clouston

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Rivastigmine for gait stability in patients with Parkinson's disease (ReSPonD)

Authors: Henderson EJ et al.

Summary: Patients with PD who had fallen on ≥1 occasion in the prior year but were able to walk 18m without an aid were randomised to receive oral rivastigmine uptitrated from 3 mg/day to a target of 12 mg/day over 12 weeks (evaluable n=55) or placebo (evaluable n=59) in this phase 2 trial. The primary endpoint was difference in step-time variability, measured with a triaxial accelerometer during an 18m walking task, under the following three conditions: i) normal walking; ii) walking while naming words beginning with a single letter (simple dual task); and iii) walking while naming words, alternating between two letters of the alphabet (complex dual task). Compared with placebo, rivastigmine recipients had significantly improved step-time variability for normal walking by week 32 (ratio of geometric means 0.72 [95% CI 0.58–0.88]) and for the simple dual task (0.79 [0.62–0.99]), but not for the complex dual task (0.81 [0.60–1.09]), and rates of nausea (31% vs. 5%) and vomiting (17% vs. 5%) were greater.

Comment: Falls are a late complication of PD and occur for a number of reasons. One reason for falls is that 'step-time variability' worsens with time and is thought to be related to cholinergic deficiency. This randomised, double-blind, placebo-controlled trial showed that rivastigmine could improve step-time variability in PD patients compared with placebo. None of the patients had dementia. Results of phase 3 trials are awaited, including an assessment of frequency of falls. If rivastigmine can decrease the frequency of falls, it will be useful to offer it to PD patients with refractory falls. What is concerning is the high frequency of gastrointestinal side effects in the rivastigmine group.

Reference: Lancet Neurol 2016;15(3):249–58

Abstract

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GPi vs STN deep brain stimulation for Parkinson disease

Authors: Odekerken VJJ et al., for the NSTAPS study group

Summary: This paper described 3-year follow-up outcomes of 128 patients with PD who were randomised to bilateral DBS of the GPI or STN; 90 participants completed the 3-year follow-up. Compared with GPI-DBS, STN-DBS was associated with significantly greater motor symptom improvement with a lower median UPDRS score (first coprimary outcome; 28 vs. 33 [p=0.04]), but no significant difference for the composite of cognitive, mood and behavioural effects and inability to complete 36 months of follow-up (second coprimary outcome; 86% vs. 83%). STN-DBS was also associated with a greater improvement in off-drug functioning compared with GPI-DBS, as assessed by mean AMC Linear Disability Scale score (72.6 vs. 65.2 [p=0.05]), and a lower median levodopa equivalent dose at 3 years (605 vs. 1060mg [p<0.001]). With the exception of more reoperations to a different target after GPI-DBS than after STN-DBS (8 vs. 1), there were no significant between-group differences in adverse events.

Comment: The optimal site for targeting for DBS (STN versus GPI) remains controversial, despite a number of published studies. Most units still favour STN as the target. STN targeting is thought to allow greater postoperative medication reduction, but carries a greater risk of behavioural side effects. This randomised study with 3 years of follow-up showed better off-phase motor improvement with STN targeting, but no differences in cognitive or behavioural side effects between STN and GPI. Based on this study, STN is likely to remain the favoured target.

Reference: Neurology 2016;86(8):755–61
Abstract

Physiotherapy and occupational therapy vs no therapy in mild to moderate Parkinson disease

Authors: Clarke CE et al., for the PD REHAB Collaborative Group

Summary: Patients with mild-to-moderate PD and limitations in activities of daily living were randomised to physiotherapy and occupational therapy (n=381) or no therapy (n=381) in this trial. Compared with no therapy, the intervention was associated with a borderline favourable EuroQol-5D quotient at 3 months (p=0.04), but there was no significant between-group difference for NEADL (Nottingham Extended Activities of Daily Living) scale total score (p=0.41) or PDQ-39 (Parkinson's Disease Questionnaire-39) summary index score (p=0.99). Repeated measures analyses revealed no difference in NEADL total score, but small differences in favour of the intervention were apparent for PDQ-39 summary index and EuroQol-5D scores (respective p values 0.005 and 0.04). Adverse events did not differ between study arms.

Comment: This study has generated a lot of controversy, including criticism from allied health professionals, as it failed to show any immediate (3-month) or interim (15-month) clinically meaningful improvement in activities of daily living or QOL in mild-to-moderate PD for patients receiving physiotherapy and occupational therapy. The allied health intervention was 'low dose' (median therapist contact time was four visits of 58 minutes over 8 weeks). This result is not surprising, as the allied health interventions were not intense. Also in early or moderate PD, disability may be minimal or stable for a long time. A study looking at the effect of physiotherapy and occupational therapy interventions in PD patients with more advanced disease would have been more valuable.

Reference: JAMA Neurol 2016;73(3):291–9
Abstract

Parkinson's Disease Research Review™

Independent commentary by Dr Paul Clouston, MB.BS. PhD FRACP

Paul is a general neurologist with interest in PD and neuromuscular disease. He is currently retired from practice for health reasons, but remains an affiliate at Brain-Mind Institute Parkinson's Research Clinic since 2013, and was a senior neurologist for Westmead Hospital, Western Sydney. He has extensive experience in general neurological practice and teaching neurological research, including clinical trials and publications, and has previous general management experience working as acting head of Westmead Department of Neurology, Director of EMG laboratory and an organiser of undergraduate medical student teaching.

BOC0272b/UC October 2015

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Postoperative apathy can neutralise benefits in quality of life after subthalamic stimulation for Parkinson's disease

Authors: Martinez-Fernandez R et al.

Summary: The impact of postoperative apathy on health-related QOL was investigated in 88 patients with PD who had undergone STN-DBS; 27.1% exhibited apathy 1 year postsurgery according to the Starkstein scale. There was no significant difference in decreases in UPDRS motor scores between the apathetic and nonapathetic patients (–40.4% vs. –48.6%), and there was no improvement in PDQ-39 score among apathetic patients versus a significant improvement in nonapathetic patients (–5.5% vs. –36.7%). A significant correlation was seen between apathy score changes and health-related QOL score changes (r=0.278 [p=0.009]). Patients with apathy exhibited no significant changes in baseline depression and anxiety scores (respective p values 0.409 and 0.075), whereas significant improvements were seen in the group with no apathy (respective p values 0.006 and ≤0.001). Changes in apathy were significantly correlated with changes in depression (r=0.594 [p≤0.001]).

Comment: Most of the neuropsychiatric side effects of STN-DBS (e.g. mania or depression) settle within 6 months. Postoperative apathy is an underappreciated yet potentially devastating long-term complication that can negate the benefits of any postoperative improvement in movement. This study found an alarmingly high rate (27.1%) of apathy in 88 patients who had STN-DBS 12 months earlier. The possibility of long-term worsening apathy should be discussed with every PD patient considering STN-DBS.

Reference: J Neurol Neurosurg Psychiatry 2016;87(3):311–8
Abstract

DAT imaging and clinical biomarkers in relatives at genetic risk for LRRK2 R1441G Parkinson's disease

Authors: Bergareche A et al.

Summary: This research investigated motor and nonmotor symptoms and striatal dopaminergic denervation, and the relationship between them, in a cohort of asymptomatic relatives of patients with PD with the *LRRK2* (leucine-rich repeat kinase 2) R1441G mutation; 27 of the asymptomatic relatives carried the mutation and 19 did not. The researchers used ^{123}I-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)-nortropane SPECT binding ratios to evaluate striatal, putamenal and caudate dopaminergic transporters. Carriers of the *LRRK2* R1441G mutation had significantly lower ^{123}I-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)-nortropan mean striatal (p=0.03), mean putamenal (p=0.01) and lowest putamenal (p=0.01) binding ratios than noncarriers. A multiple linear regression analysis revealed that *LRRK2* R1441G mutation carrier status and the execution of timed tests were significant predictors of striatal ^{123}I-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)-nortropane binding; the proportions of variation accounted for by the regression model of these variables were 69% and 53% for the putamen and caudate nucleus, respectively.

Comment: This is an interesting study looking at relatives of patients with PD who carried the *LRRK2* R1441G mutation. For 27 relatives who were asymptomatic carriers of the mutation, there was a correlation between loss of striatal and putamenal dopamine transporters on SPECT and worsening execution of timed motor tasks. Further longitudinal evaluation of this asymptomatic cohort is awaited.

Reference: Mov Disord 2016;31(3):335–43
Abstract

Association between change in body mass index, Unified Parkinson's Disease Rating Scale scores, and survival among persons with Parkinson disease

Authors: Wills A-MA et al., for the NINDS Exploratory Trials in Parkinson Disease (NET-PD) Investigators

Summary: With the aim of exploring associations between changes in BMI, UPDRS motor and total scores and PD survival, these authors conducted a secondary analysis of 3- to 6-year data from the NINDS Exploratory Trials in Parkinson Disease long-term study 1 (in which participants with early, treated PD were randomised to receive creatine monohydrate or placebo). Among the 1673 participants, BMI decreased in 9.4% and increased in 13.9%. Compared with participants with stable bodyweight, those who lost weight had a 1.48-point greater UPDRS score increase per visit after adjustment for covariates (p<0.001) and those who gained weight had a 0.51-point relative decrease per visit (p=0.03). An unadjusted difference in survival across the three BMI groups lost statistical significance after adjustment for covariates.

Comment: Some patients presenting with PD lose bodyweight as their PD deteriorates. This study confirmed this association. In a large group of PD patients, the researchers identified a group who had decreasing BMI over 3- to 6-year follow-up. In this group, compared with the groups who gained weight or whose weight was stable, there was a correlation between worsening weight loss and deteriorating UPRDS scores but not with survival. This study shows that loss of weight in PD is an important symptom.

Reference: JAMA Neurol 2016;73(3):321–8
Abstract

Induction of α-synuclein aggregate formation by CSF exosomes from patients with Parkinson's disease and dementia with Lewy bodies

Authors: Stuendl A et al.

Summary: To test the hypothesis that exosomal α-synuclein species from patients with α-synuclein-related neurodegeneration serve as carriers for interneuronal disease transmission, these researchers isolated exosomes from the CSF of patients with PD, dementia with Lewy bodies, progressive supranuclear palsy (as a non-α-synuclein-related disorder with clinical overlap with PD) and neurological controls. They analysed CSF exosome numbers and α-synuclein protein content, and their potential to induce oligomerisation of α-synuclein. There were differences between patients with PD and those with dementia with Lewy bodies for the quantification of CSF exosomal α-synuclein, and there was a correlation between exosomal α-synuclein level and cognitive impairment severity in cross-sectional samples obtained from the patients with dementia with Lewy bodies. Of note, CSF exosomes derived from patients with PD and dementia with Lewy bodies were found to dose dependently induce α-synuclein oligomerisation in a reporter cell line.

Comment: There is increasing evidence that the interneuronal propagation of 'misformed' 'toxic' α-synuclein is involved in the pathogenesis of the synucleinopathies. This group was able to demonstrate that CSF exosomes (containing α-synuclein) from patients with PD and dementia with Lewy bodies could alter 'standard' α-synuclein to possibly spread the disease pathology within the CNS.

Reference: Brain 2016;139(2):481–94
Abstract

Frequency and profile of Parkinson's disease prodromi in patients with malignant melanoma

Authors: Walter U et al.

Summary: Early markers of PD were investigated in patients with high-risk cutaneous (n=53) or uveal (n=12) melanoma versus 35 control subjects. There were greater frequencies of substantia nigra hyperechogenicity and prodromal motor and nonmotor features of PD, especially asymmetric motor slowing and apathy, among the patients with melanoma, but hyposmia and colour vision disturbances were infrequent. A correlation was identified between greater substantia nigra echogenicity and lower serum iron level in patients with melanoma. All participants with mild or definite parkinsonism diagnosed after 1 year had substantia nigra hyperechogenicity plus motor asymmetry or hyposmia at baseline. A specific relationship was seen between parkinsonism and melanoma located in the sun-exposed skin of the head or neck.

Comment: This was a prospective blinded study looking for evidence of prodromal and diagnostic features of PD in patients with a history of melanoma. Prodromal markers of PD were increased in this cohort, confirming a previously known epidemiological association between the PD and melanoma. If possible, follow-up of those patients with a history of melanoma and 'prodromal markers of PD' is awaited.

Reference: J Neurol Neurosurg Psychiatry 2016;87(3):302–10
Abstract

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Alpha-synuclein in gastric and colonic mucosa in Parkinson's disease: limited role as a biomarker

Authors: Chung SJ et al.

Summary: This research conducted in 38 patients with PD, 13 with probable multiple system atrophy and 53 healthy controls sought to determine if α-synuclein immunoreactivity from gastric and colonic mucosal tissues obtained by routine endoscopy was able to detect PD, and also to examine the pathological burden of α-synuclein with motor and nonmotor PD features. There was no significant difference across the three participant groups for enteric α-synuclein immunoreactivity, but there were higher frequencies of positive α-synuclein immunoreactivity in biopsy samples from the stomach than from the colon for all three groups (31.6–40.0% vs. 8.0–18.5% [p<0.05]). There was no significant correlation between α-synuclein immunoreactivity and motor or nonmotor features of PD.

Comment: The presence of Lewy bodies (containing α-synuclein) in the wall of the gastrointestinal tract of some patients with PD has stimulated interest in the gut as a possible portal for the pathogenesis of PD. This study showed no differences in α-synuclein reactivity in biopsies taken from the stomach and colon from patients with PD, patients with probable multiple system atrophy and controls, casting doubt on the utility of biopsies from the gut to find a diagnostic biomarker of PD.

Reference: Mov Disord 2016;31(2):241–9
Abstract

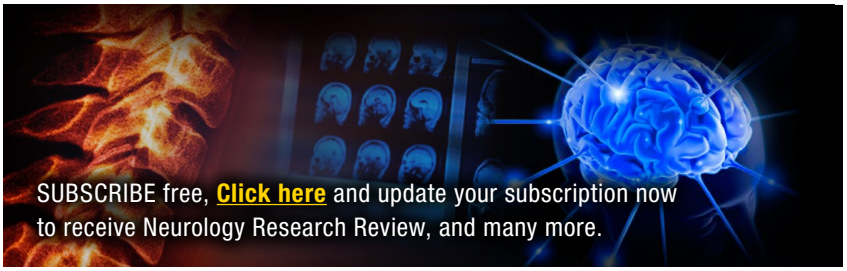
Peripheral synucleinopathy in early Parkinson's disease: submandibular gland needle biopsy findings

Authors: Adler CH et al.

Summary: This research sought to determine if submandibular gland needle biopsy findings are associated with Lewy type α-synucleinopathy in 25 patients with early PD (mean duration 2.6 years), with ten healthy control subjects as comparators; inadequate glandular tissue was obtained from six patients with PD and one control subject. Tissue staining for α-synuclein was positive in 74% of the patients with PD and 22% of the controls. No clinical differences were seen between PD-positive and -negative cases. Minor, transient adverse events (mainly swelling and bruising) occurred in 77% of cases.

Comment: This was a small study looking at α-synuclein reactivity in submandibular gland biopsies of patients with early PD (<5 years duration). It suggested there may be diagnostic value in this procedure, but larger follow-up studies are needed with all submandibular gland biopsies taken at presentation of PD.

Reference: Mov Disord 2016;31(2):250–6
Abstract



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References: 1. Sifrol and Sifrol ER Approved Product Information, August 2015. **2.** Schapira AHV *et al. Neurology* 2011;77:767–774. **3.** Poewe WM *et al. Neurology* 2011;77:759–766. Boehringer Ingelheim Pty Ltd, ABN 52 000 452 308, 78 Waterloo Road, North Ryde, NSW 2113. ® Registered trademark Boehringer Ingelheim. AU/SIF-121061c. BOC0272c/UC. Date prepared October 2015.

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