Parkinson's Disease Research Review™

Making Education Easy

Issue 13 – 2014

In this issue:

Abbreviations used in this issue:

DBS = deep-brain stimulation; **FOG** = freezing of gait; **LED** = levodopa equivalency dose; **OCT** = optical coherence tomography; **PD** = Parkinson's disease; **STN** = subthalamic nucleus; **UPDRS** = Unified PD Rating Scale

Welcome to the thirteenth issue of Parkinson's Disease Research Review.

This issue includes research suggesting a greater focus is needed on increasing general ambulatory activity and exercise among patients with PD from the time of diagnosis. Australian research is included, with study findings supporting the role of impaired communication between complementary yet competing neural networks in FOG. UK researchers have reported improved survival associated with STN-DBS in patients with advanced PD. This issue concludes with a fascinating OCT study linking retinal nerve fibre layer thickness with visual hallucinations in patients with PD.

I hope you enjoy the selection for the first issue of 2014. Please feel free to send your comments, feedback and suggestions.

Kind Regards,

Dr Kelly Bertram

kelly.bertram@researchreview.com.au

Effect of subthalamic nucleus deep brain stimulation on driving in Parkinson disease

Authors: Buhmann C et al.

Summary: These researchers undertook a comparison of driving performance among 23 patients with PD who had undergone DBS, 21 who had not and 21 controls, and they also compared the respective effects of stimulation and levodopa on driving performance. Three tests were undertaken in the medicated DBS cohort under three different conditions: i) 'stimulation on' (equated to daily treatment); ii) 'stimulation off'; and iii) 'stimulation off with levodopa at a dosage aimed at maintaining motor status. Driving performance was negatively affected by age and cognitive effects. Compared with controls, participants who had not undergone DBS performed worse with respect to driving time and errors, while participants who underwent DBS drove slower but had comparable safety performance. Compared with participants who did not undergo DBS, those who did drove slower and exhibited superior safety. Among the group of participants who underwent DBS, more accurate driving was seen with the 'stimulation on' condition than in levodopa recipients, but no difference was seen for motor effects. Compared with the 'stimulation off' condition, driving was superior in the 'on' condition, but not with levodopa therapy.

Comment: This German study aimed to determine the effect of STN-DBS on driving ability in PD using a driving stimulator capable of recording steering, indicator use and accelerator/brake signals after presentation of various driving tasks. Drivers were given the opportunity to test drive in a virtual car park prior to undergoing three fixed sequence test runs under different treatment conditions. Driving error number and standardised severity of error were recorded in each scenario. Higher disease severity was associated with longer total driving time but a reduced error rate. Total LED and duration of DBS stimulation did not correlate with any driving parameter. Overall, the researchers found DBS treatment was associated with a lesser error rate than levodopa, despite similar motor improvement, possibly suggesting differing effects on cognition, attention and procedural learning. Of note, the patients with DBS had an average disease duration of 14 ±5 years, as compared with the no-DBS group at 6 ±5 years, a higher average Hoehn and Yahr stage, and consequently a higher daily LED (778 ±400 vs. 647 ±412mg).

Reference: Neurology 2014;82(1):32–40

http://www.neurology.org/content/82/1/32.abstract

Ambulatory activity in incident Parkinson's: more than meets the eye?

Authors: Lord S et al.

Summary: Patients with newly diagnosed PD and controls (respective n values 89 and 97) wore an activity monitor for 7 days in this study. Significant differences were seen between the groups for total steps, accumulation of bout length and variability ($p<0.001$ for all). Compared with controls, patients with PD spent significantly less time undertaking >2-minute bouts of walking, due to fewer long bouts, rather than less time walking during each bout. Weak but significant correlations were seen for a range of characteristics and sustained walking both in patients with PD and controls. Fewer patients with PD achieved the recommended 30 minutes of walking each day, comprised of >10-minute ($p=0.02$) and >2-minute bouts ($p<0.001$).

Comment: Yet another study showing people with PD do not engage in regular physical activity, even when they are aware their time spent walking is being objectively measured. Even with very early stage (Hoehn and Yahr stage 1) disease, these participants avoided prolonged walking, with only 3% of those with PD in this study achieving the minimum recommended 30 minutes of walking per day, even with all bouts of walking >10 minutes added together. (To be fair, only 12% of healthy control subjects achieved this!) With a growing body of evidence for the benefit of regular exercise in preventing falls and maintaining longevity in PD, this serves as a reminder to treating clinicians to build into our patient management discussions, the need to encourage regular physical activity.

Reference: J Neurol 2013;260(12):2964–72
http://link.springer.com/article/10.1007/s00415-013-7037-5

RESEARCH REVIEW™
the Australian perspective

Motor fluctuations and *Helicobacter pylori* in Parkinson's disease

Authors: Rahne KE et al.

Summary: The impact of gastrointestinal tract *Helicobacter pylori* on levodopa absorption was investigated in 75 patients with PD of ≥4 years' duration. Propensity matched analyses compared data between patients with gastrointestinal *H. pylori* infection (n=20) and matched controls. Although no difference was seen between *H. pylori*-infected and noninfected patients for LED, *H. pylori*-infected patients had a significantly lower average total UPDRS score (4.8 vs. 7.7; $p=0.05$) and significant decreases in wearing-off and sleep disturbances ($p<0.05$). No difference was seen between *H. pylori*-infected and noninfected patients for vitamin B_{12}, folic acid or homocysteine levels.

Comment: This study is similar to previous studies reported by other groups, with differing interpretations. Lee WY et al. reported a similar study ('*Helicobacter pylori* infection and motor fluctuations in patients with PD' Mov Disord 2008;23[12]:1696–700) demonstrating that treatment of *H. pylori* infection reduced motor fluctuations, and suggested *H. pylori* infection interfered with intestinal levodopa absorption. This was retested by Fasano A et al. ('The role of small intestinal bacterial overgrowth in Parkinson's disease' Mov Disord 2013;28[9]:1241–9). A Cochrane review on this issue concluded there was a lack of evidence for *H. pylori* treatment in PD given the sample sizes in the studies reported to date. This study suggested *H. plyori* may be protective against motor fluctuations, but again included small numbers and failed to determine the extent to which this common bacterial infection may influence variability in treatment response.

Reference: J Neurol 2013;260(12):2974–80
http://link.springer.com/article/10.1007/s00415-013-7089-6

Parkinson's Disease
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Independent commentary by Dr Kelly Bertram a movement disorders neurologist based at the Alfred Hospital. She is actively engaged in research in neurodegenerative disease including Parkinson's disease, progressive supranuclear palsy and multiple system atrophy, and in dystonia.

Freezing of gait in Parkinson's disease is associated with functional decoupling between the cognitive control network and the basal ganglia

Authors: Shine JM et al.

Summary: Impairment of communication between distributed neuronal networks was compared between ten patients with PD and FOG and 10 matched controls with no FOG. All participants performed a virtual reality gait task 'on' and 'off' their regular dopaminergic medication. While all participants employed their left cognitive control network and the ventral attention network during all task performances, and also exhibited increased connectivity between the bilateral cognitive control networks, only those with FOG showed functional decoupling between their basal ganglia network and the cognitive control network in each hemisphere, which was also associated with paroxysmal motor arrests.

Comment: Led by Assoc Prof Simon Lewis, this elegant study by our Sydney colleagues used functional magnetic resonance imaging to actively assess brain function during a virtual reality walking task in PD patients prone to FOG. It adds to the data suggesting FOG is related to impaired executive functioning and the presence of increased cognitive load, and expands on previous studies suggesting frontoparietal cortical dysfunction by revealing impairment of communication between cortical and subcortical structures at the time of FOG.

Reference: Brain 2013;136(12):3671–81
http://brain.oxfordjournals.org/content/136/12/3671.abstract

Deep brain stimulation improves survival in severe Parkinson's disease

Authors: Ngoga D et al.

Summary: The impact of STN-DBS on survival was explored in patients with PD given the choice of undergoing surgery (n=106) or continued medical therapy (controls; n=41). Compared with controls, participants who underwent STN-DBS survived significantly longer (adjusted hazard ratio 0.29 [95% CI 0.13–0.64]) and were significantly less likely to require residential care home admission (adjusted odds ratio 0.1 [0.0–0.3; p<0.001]).

Comment: This is an interesting long-term follow-up study of patients undergoing surgical treatment for moderately advanced PD. It showed a useful long-term benefit of surgery not just for symptom management, but in improving mortality in PD. The link between entering nursing home care and increased mortality has been documented previously in PD. Unfortunately, those choosing not to have surgery did not undergo neuropsychological testing and we do not know if there were cognitive deficits that may have influenced the 'patients' choice not to undergo surgery in the medical treatment only group. It is therefore possible that the medical only group were a more cognitively affected population, influencing their entry to nursing home care and therefore mortality. Despite these missing data, this is a useful study to consider when counselling patients with moderate-to-advanced PD who may be suitable for surgery.

Reference: J Neurol Neurosurg Psychiatry 2014;85(1):17–22
http://jnnp.bmj.com/content/85/1/17.abstract

PREDICT-PD: Identifying risk of Parkinson's disease in the community

Authors: Noyce AJ et al.

Summary: These authors estimated the future PD risk by systematic review of risk factors and early features of PD in self-referred patients aged 60–80 years with the disease who completed an online survey (n=1324), a keyboard-tapping task (n=1146) and University of Pennsylvania Smell Identification Tests (n=1065). Compared with the 100 lowest risk score participants, the 100 highest risk participants had a significantly lower median smell test score (30 vs. 33/40; p<0.001), significantly fewer key taps in 30 sec (55 vs. 58; p=0.045) and a significantly greater proportion of those above the cutoff for REM-sleep behaviour disorder (24% vs. 10%; p=0.008). Regression analyses revealed associations between increasing risk scores and worse scores in these three metrics across the entire group (p≤0.001).

Comment: Attempts to identify those at the highest risk of developing PD in the future require prescreening of large population cohorts and significant resources. This would be a useful group to test emerging diagnostic tests for PD and possibly disease-modifying treatments were they to become available. This group has taken a unique approach to population screening, which is less resource intensive and may still enrich the 'high-risk' group, by utilising an online portal allowing the participants to be screened remotely with minimal clinician input. It used a keyboard tapping task to replicate the paper-based tap test and measure for possible bradykinesia in addition to an online survey for known risk factors, followed by a standardised smell test sent to the participants' homes. This requires follow-up to determine the utility of this method in finding a high-risk group, but demonstrates practical use of available technology, and if successful could easily be replicated in a standardised way across many countries.

Reference: J Neurol Neurosurg Psychiatry 2014;85(1):31–7
http://jnnp.bmj.com/content/85/1/31.full

Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease

Authors: Olanow CW et al., for the LCIG Horizon Study Group

Summary: Adults with advanced PD underwent jejunal placement of a percutaneous gastrojejunostomy tube and were randomly assigned to receive levodopa-carbidopa via an immediate-release oral (n=31) or an intestinal gel infusion formulation (n=35), along with placebo via the required route of administration to achieve blinding. Compared with the oral group, the intestinal gel group had a significantly greater decrease in mean 'off' time at 12 weeks (4.04 vs. 2.14h; p=0.0015) and a significantly greater increase in mean 'on' time without troublesome dyskinesia (4.11 vs. 2.24h; p=0.0059). The respective overall adverse event rates in the intestinal gel and oral levodopa arms were 95% and 100%, with respective serious adverse event rates of 14% and 21%, mainly associated with the percutaneous gastrojejunostomy tube.

Comment: This study directly compared two different modes of levodopa delivery in a double-blind fashion, and demonstrated improved 'on' time without troublesome dyskinesias in those on continuous therapy. This highlights the potential advantages of this treatment strategy in advanced PD. As with all studies of intestinal gel levodopa-carbidopa, the main adverse events related to the tube itself, and continue to highlight the need for an experienced team in managing advanced treatment modalities in PD.

Reference: Lancet Neurol 2014;13(2):141–9
http://tinyurl.com/lb52trd

Cognitive and motor function in long-duration *PARKIN*-associated Parkinson disease

Authors: Alcalay RN et al.

Summary: Cognitive and motor performances were compared in patients with PD of >14 years' duration who were homozygous (n=4) or compound heterozygous (n=17) for two *PARKIN* mutations versus noncarriers (n=23) in this cross-sectional study. Compared with noncarriers, *PARKIN* carriers had significantly earlier ages of PD onset and examination ($p \leq 0.004$), but performed significantly better in Mini-Mental State Examination and Clinical Dementia Rating assessments ($p \leq 0.01$). Multivariate analyses showed that *PARKIN* carriers performed better than noncarriers in UPDRS-III assessments and attention, memory and visuospatial cognitive domain tests ($p \leq 0.03$).

Comment: These are early data of a small cohort of people with early-onset PD, divided into those with and without *PARKIN* gene mutations. The results suggest lesser rates of cognitive impairment in *PARKIN* carriers, who had longer disease duration but lesser motor impairment than the non-PARKIN group. The differences seen between these groups were mild, but an extensive battery of neuropsychological tests has been performed with the intention of ongoing follow-up. This is relevant for those who are interested in 'splitting' this complex condition into phenotypes to better understand the variability in patient progression. This may start to give us the capacity to more reliably counsel our patients in the future about how PD will affect them personally.

Reference: JAMA Neurol 2014;71(1):62–7
http://archneur.jamanetwork.com/article.aspx?articleid=1763961

Retinal nerve fiber layer thickness and visual hallucinations in Parkinson's Disease

Authors: Lee J-Y et al.

Summary: In order to explore the relationship between retinal thinning and visual hallucinations, this research used spectral domain OCT to compare 61 case patients with PD with 30 healthy controls. The patients with PD had significant parafoveal inner nuclear layer thinning compared with controls, while other retinal layers did not differ. Among the patients with PD, those who also had visual hallucinations without dementia had the thinnest retinal nerve fibre layer, followed by those with hallucinations with dementia, and then those with neither hallucinations nor dementia. No significant correlations were seen between general ophthalmological examination findings and visual hallucinations, or between retinal thicknesses and duration or severity of PD and medication dosages.

Comment: This is one of three articles in the January 2014 edition of the Movement Disorders journal looking at the use of OCT measurements in contributing to our understanding of PD. It is known there are dopaminergic cells in the retina, and that contrast sensitivity is altered in PD, which may relate to loss of dopamine in the retina itself. The wider availability of OCT scans allows more accurate measurement of histological layers of the retina *in vivo*, which can be compared over time in patients developing visual consequences of PD. This study found the retinal layer to be thinner in PD with reported visual hallucinations, greatest in those with concurrent dementia. In line with previous reports on the relationship between levodopa dose and hallucinations, there was a trend to higher LED in these patients also, although not significant. Although this is a small study, it shows the potential value of this technology in measuring one population of dopaminergic cells available for noninvasive testing.

Reference: Mov Disord 2014;29(1):61–7
http://onlinelibrary.wiley.com/doi/10.1002/mds.25543/full

