Parkinson's Disease Research Review™

Making Education Easy

Issue 12 – 2013

In this issue:

Abbreviations used in this issue:

DBS = deep-brain stimulation
FOG = freezing of gait
GPI = globus pallidus interna
PD = Parkinson's disease
STN = subthalamic nucleus

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

In this issue, research from the US provides evidence that patients with PD with FOG have comorbid increased muscle activity during REM sleep. UK research suggests that inhaled apomorphine for treating 'off' periods in PD has the potential to replace intermittent subcutaneous self-injections, which sometimes cause cutaneous effects; an excellent review on the efficacy of this agent in the management of nonmotor aspects of PD is also included. This issue concludes with a BMJ paper reporting no increased risk of suicidal ideation or behaviours associated with DBS to the STN or GPI.

I hope you enjoy the selection for this issue. I look forward to receiving your comments and feedback.

Kind Regards,

Dr Simon Sung

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Driving and off-road impairments underlying failure on road testing in Parkinson's disease

Authors: Devos H et al.

Summary: Driving skills and off-road evaluations of 104 active, licensed drivers with PD were evaluated in this cross-sectional study. The respective pass and fail rates were 65% and 35%. Lateral positioning at low speed, speed adaptations at high speed and left turning manoeuvre performance resulted in a model that best determined the pass/fail outcome (R^2=0.56). Participants who failed the on-road evaluations had worse results for motor, visual and cognitive tests. A multivariate analysis revealed that measures of visual scanning, motor severity, PD subtype, visual acuity, executive functions and divided attention independently predicted pass/fail outcomes (R^2=0.60).

Comment: In this cross-sectional study of 104 active, licensed drivers with PD, in addition to reporting the clinical characteristics that were most likely to be associated with failure of on-road testing, Devos et al. went one step further and identified that impairments in three specific driving skills – lane positioning, speed adaptation at higher speed and turning across oncoming traffic (turning left in America) – most strongly contributed to driving test failure. This is the first study to examine which driving skill impairments cause driving test failure in PD patients and provides therapists with a framework for developing driving rehabilitation strategies in the future. Another interesting finding in this study is the lack of difference in pass/fail rates between participants who were noted to have driving problems versus those who did not report driving problems, suggesting that many PD patients with poor driving performance may go unrecognised.

Reference: Mov Disord; Published online Oct 24, 2013
http://onlinelibrary.wiley.com/doi/10.1002/mds.25701/abstract

Increased REM sleep without atonia in Parkinson disease with freezing of gait

Authors: Videnovic A et al.

Summary: These researchers conducted overnight polysomnography in participants with: i) REM sleep behaviour disorder; ii) PD without FOG; iii) PD with FOG; and iv) controls. No significant differences were seen between PD patients with and without FOG for disease severity or duration of dopaminergic medications. Compared with controls and PD patients without FOG, PD patients with FOG and those with REM sleep behaviour disorder had significant increases in tonic muscle activity, but there were no significant tonic EMG differences seen between the PD patients with FOG and REM sleep behaviour disorder groups, or tonic or phasic EMG differences between the PD patients without FOG and the control groups. Phasic muscle activity was significantly increased in the REM sleep behaviour disorder group versus the other groups (p=0.029) and in the PD with FOG versus the control group (p=0.001), but not between the PD with and without FOG groups (p=0.059).

Comment: In this study, Videnovic et al. demonstrated that PD patients with FOG had a marked increase in REM sleep without atonia compared with PD patients without FOG, and that the degree of REM sleep without atonia was similar to that seen in patients with REM sleep behaviour disorder. From this, they postulated that the presence of REM sleep without atonia may be predictive of the development of PD with FOG. Also, the findings in this study provide additional support to the hypothesis that FOG in PD and REM sleep without atonia in patients with REM sleep behaviour disorder may share common pathophysiological mechanisms – namely involving the pedunculopontine nucleus and locus coeruleus.

Reference: Neurology 2013;81(12):1030–5
http://www.neurology.org/content/81/12/1030

Levodopa challenge test and ^{123}I-metaiodobenzylguanidine scintigraphy for diagnosing Parkinson's disease

Authors: Asayama S et al.

Summary: These researchers investigated the sensitivity and specificity of an acute levodopa challenge test in 45 consecutive patients with extrapyramidal symptoms, with 32 also undergoing ^{123}I-metaiodobenzylguanidine myocardial scintigraphy for comparison. Clinically definite PD was diagnosed in 22 of the participants during ≥24 months of follow-up. The acute levodopa challenge test predicted clinical PD with sensitivity and specificity of 81.8% and 81.8%, respectively, compared with respective values of 62.5% and 62.5% for ^{123}I-metaiodobenzylguanidine myocardial scintigraphy. Furthermore, the acute levodopa challenge test was associated with better sensitivity than ^{123}I-metaiodobenzylguanidine myocardial scintigraphy in both early- and middle-stage PD.

Comment: The clinical diagnosis of idiopathic PD, particularly in its early stages, can often be incorrect, and attempts in the past to improve diagnostic accuracy with various tests and procedures have generally been unrewarding. The situation has not changed much despite this latest attempt by Asayama et al., who concluded that the sensitivity and specificity of cardiac ^{123}I-metaiodobenzylguanidine scintigraphy was inferior to an acute levodopa challenge for the early diagnosis of idiopathic PD. They did point out that the acute levodopa challenge had reasonable sensitivity and specificity for diagnosing idiopathic PD in its early stages, although it can be associated with increased side effects and cost compared with a chronic challenge.

Reference: Acta Neurol Scand 2013;128(3):160–5
http://onlinelibrary.wiley.com/doi/10.1111/ane.12104/abstract

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Independent commentary by Dr Simon Sung, a neurologist at the Royal Melbourne Hospital and Western Hospital in Melbourne.

His main interest is in Movement Disorders, and is currently undertaking a PhD in the University of Melbourne on the topic of 'Pain in Parkinson's Disease'.

Levodopa infusion improves impulsivity and dopamine dysregulation syndrome in Parkinson's disease

Authors: Catalán MJ et al.

Summary: This paper reported on eight patients with PD with uncontrolled motor complications, severe impulsivity and dopamine dysregulation syndrome who were treated with 15-hour, daytime jejunal infusions of levodopa 1007.2 ±302.5 mg/day. Assessments at 25 ±9 weeks of treatment with a stable dose showed significant decreases from baseline in 'off' periods and dyskinesias, and near complete resolution of all types of impulse control disorders and dopamine dysregulation syndrome in all participants. Five participants exhibited improvement in punding, but complete resolution was seen in only one participant.

Comment: In this case series of eight patients who had dopamine agonist-induced impulse control disorders and/or levodopa-induced dopamine dysregulation syndrome, replacement of oral medications with intrajejunal infusion of levodopa resulted in a marked improvement in both impulsivity and dopamine dysregulation. Whilst this study did not address the specific mechanism of action responsible for this improvement, it is in line with the hypothesis that continuous dopaminergic therapy may help reverse the aberrant neural plasticity responsible for increased impulsivity caused by sensitisation of dopaminergic receptors to pulsatile oral dopaminergic therapy.

Reference: Mov Disord; Published online Oct 10, 2013
http://onlinelibrary.wiley.com/doi/10.1002/mds.25636/abstract

Inhaled dry powder apomorphine (VR040) for 'off' periods in Parkinson's disease

Authors: Grosset KA et al.

Summary: Patients with PD in 'off' state were randomised 2:1 to receive inhaled dry powder apomorphine (VR040) 1.5mg, 2.3mg, 3.0mg or 4.0mg until efficacy was achieved or placebo in this dose-ranging study. The mean improvement in UPDRS (Unified PD Rating Scale) part 3 score was significantly greater in the apomorphine recipients than the placebo recipients (26.8 vs. 14.9 points; p=0.016). The rapid absorption of apomorphine over 2–7 min translated to reversal from the 'off' state in a mean of 10 min. Adverse events were similar between apomorphine and placebo.

Comment: Apomorphine injected subcutaneously is currently the quickest method of relieving disabling motor 'off' periods in PD, with an onset of action of about 14 minutes. However, adverse cutaneous reactions can be problematic, and there have been a few recent attempts to examine the viability of delivering apomorphine via different routes, including this latest dose-ranging study using inhaled apomorphine in a dry powder form. The preliminary results are encouraging, with inhaled apomorphine achieving a clinically meaningful UPDRS3 improvement, a rapid onset of action (average of 10 min) and a low incidence of adverse events. Further studies are warranted to further investigate its efficacy and tolerability.

Reference: Acta Neurol Scand 2013;128(3):166–71
http://onlinelibrary.wiley.com/doi/10.1111/ane.12107/abstract

Prevalence and features of peripheral neuropathy in Parkinson's disease patients under different therapeutic regimens

Authors: Mancini F et al.

Summary: These researchers reported that peripheral neuropathy with no evident cause was seen in 28%, 20% and 6% of consecutive patients with PD receiving intestinal levodopa (n=50), oral levodopa (n=50) or other dopaminergic treatment (n=50), respectively, with 71%, 100% and 100% exhibiting clinical subacute sensory peripheral neuropathy. In contrast, 29% of patients receiving intestinal levodopa presented with acute motor peripheral neuropathy. Significant differences were seen between patients with versus without peripheral neuropathy for levodopa daily dose and vitamin B_{12} and homocysteine levels.

Comment: This study demonstrates that PD patients on levodopa have a higher risk of developing subacute peripheral neuropathy compared with those on other forms of dopaminergic therapy, and that this may be mediated via vitamin B_{12} deficiency and homocysteine accumulation and treatable through vitamin supplementation. Additionally, patients on continuous intestinal infusions of levodopa had an increased risk of developing an acute inflammatory peripheral neuropathy. This highlights the need for physicians to monitor for the development of neuropathy in PD patients on levodopa.

Reference: Parkinsonism Relat Disord; Published online Oct 7, 2013
http://www.prd-journal.com/article/S1353-8020%2813%2900337-4/abstract

Intraoperative dopamine release during globus pallidus internus stimulation in Parkinson's disease

Authors: Martinez RCR et al.

Summary: Using microdialysis, these researchers recorded pallidal dopamine in five patients with PD undergoing microelectrode-guided pallidotomy, and found that those with more severe disease, and therefore lower pallidal dopamine, did poorly after pallidal lesions. Dopamine levels increased during high-frequency stimulation by an average of 600% in four of the participants. While rigidity was 56% better during stimulation, such improvements did not correlate with dopamine release.

Comment: In this study, Martinez et al. examined extracellular pallidal dopamine levels using microdialysis in PD patients, and found that patients with higher pallidal dopamine levels (and correspondingly milder PD) derived a better clinical response to pallidotomy. They also attempted to investigate whether dopamine played a role in the observed clinical benefit of GPI DBS by measuring pallidal dopamine levels before, during and after acute GPI high-frequency stimulation. Whilst they did note an increase in pallidal dopamine levels with acute stimulation, this did not correlate significantly with amelioration of rigidity. Whether or not these findings apply to long-term GPI stimulation remains to be seen.

Reference: Mov Disord; Published online Oct 21, 2013
http://onlinelibrary.wiley.com/doi/10.1002/mds.25691/abstract

Subcutaneous apomorphine and non-motor symptoms in Parkinson's disease

Authors: Todorova A & Chaudhuri KR

Summary: The effects of apomorphine in nonmotor aspects of PD, including neuropsychiatric and gastrointestinal effects, sleep (including restless legs syndrome), urinary dysfunction, pain and impulse control disorders, were reviewed in this paper using data from case reports and open-label and comparative case-control studies. While data on the effect of apomorphine on nonmotor symptoms in patients with PD were limited, there was *"a strong suggestion of a beneficial effect that warrants further investigation in double-blind studies"*.

Comment: This is an excellent review article listing the currently available data of apomorphine on nonmotor symptoms in PD patients. There is a strong suggestion of a beneficial effect of apomorphine on sleep dysfunction, mood, gastrointestinal problems and urinary dysfunction. As treatment options for nonmotor symptoms in PD are quite limited, additional randomised controlled trials on the effects of apomorphine on nonmotor endpoints would be greatly welcome.

Reference: Parkinsonism Relat Disord 2013;19(12):1073–8
http://tinyurl.com/mxbu3g2

Unexplained lower limb pain in Parkinson's disease: a phenotypic variant of 'painful Parkinson's disease'

Authors: Wallace VCJ & Chaudhuri KR

Summary: Features of 22 patients with PD reporting unexplained severe proximal lower-limb pain (persistent leg pain ranging from unilateral to bilateral, and sometimes associated with whole body pain) in a survey of 225 patients were assessed using a newly devised PD pain scale. None of these patients had significant spinal pathology or evidence of large fibre neuropathy. Fourteen received regular analgesia with poor effect, and nine received morphine-based treatment; one patient with severe unremitting pain died after an accidental overdose. All the patients received a levodopa and dopamine agonist combination for PD, including three receiving intrajejunal levodopa infusions. The patients scored a mean of 17 points on a 30-point scale in a nonmotor symptom questionnaire, and 95 points on a nonmotor symptom scale that's 'normal' range was 30–60 points.

Comment: From a cohort of 225 PD patients, Wallace and Chaudhuri identified 22 who experienced unexplained unremitting proximal lower-limb pain that tended not to respond to dopaminergic optimisation or physiotherapy and was not related to fluctuations. These patients had no significant abnormalities on lumbar imaging and no evidence of large fibre neuropathy, although it was not apparent if hip imaging was performed to look for referred pain from the hip joint. The authors made the case that this cluster of patients with unremitting lower-limb pain may be suffering from a variant of PD central pain, and it should be recognised as a specific nonmotor phenotype of PD.

Reference: Parkinsonism Relat Disord; Published online Oct 21, 2013
http://www.prd-journal.com/article/S1353-8020%2813%2900346-5/abstract

Suicide ideation and behaviours after STN and GPi DBS surgery for Parkinson's disease

Authors: Weintraub D et al., for the CSP 468 Study Group

Summary: Patients with PD were randomised to DBS (n=121) or 6 months of best medical therapy (n=134) in phase 1 of the Veterans Affairs CSP 468 study, and to DBS to the STN (n=147) or GPI (n=152) in phase 2. In phase 1, no participants exhibited suicidal behaviours, and the respective new-onset suicidal ideation rates (1.9% and 0.9%; p=0.61) and proxy symptoms of relevance to suicidal ideation were similar between the DBS and best medical therapy arms. Although the 6-month suicidal ideation rates were also similar in the STN and GPI DBS arms in phase 2 (1.5% vs. 0.7%; p=0.61), several proxy symptoms were worse with STN DBS.

Comment: The association between DBS for PD and suicide has been controversial, with some case reports and observational and retrospective studies suggesting that DBS may lead to suicidal behaviours. However, in this prospective randomised controlled trial, no differences in suicidal behaviours were observed among the best medical treatment, STN DBS and GPI DBS groups 6 months postrandomisation. The authors concluded that factors such as protracted medical complications postoperatively, large decreases in dopaminergic medication and major psychiatric comorbidity were more likely to contribute to suicidal behaviours rather than electrical stimulation *per se*.

Reference: J Neurol Neurosurg Psychiatry 2013;84(10):1113–8
http://jnnp.bmj.com/content/84/10/1113

