Parkinson's Disease Research Review™

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Issue 18 – 2015

In this issue:

Abbreviations used in this review:

AD = Alzheimer's disease; **CSF** = cerebrospinal fluid; **ICD** = impulse control disorder; **NMS** = nonmotor symptoms; **PD** = Parkinson's disease; **REM** = rapid eye movement; **UPDRS** = Unified Parkinson's Disease Rating Scale

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

This issue begins with research detailing a range of prediagnostic features that can be detected in primary care patients several years before a diagnosis of PD is made. A cognitive training programme has been shown to improve processing speed, visual memory, theory of mind and functional disability in patients with PD. Italian researchers reported that action tremor is relatively common in PD, correlates with rest tremor and rigidity, and is possibly related to lower NMS burden. This issue concludes with a study showing that REM sleep behaviour disorder in PD increases the risk of developing ICD symptoms.

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

Kind Regards,

Dr Karyn Boundy

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Prediagnostic presentations of Parkinson's disease in primary care

Authors: Schrag A et al.

Summary: Associations between first presentation of prediagnostic features and a subsequent PD diagnosis were explored in this study of UK primary care patients (8166 cases and 46,755 controls). Compared with controls, patients who developed PD were more likely to have significantly higher incidences of tremor (risk ratio 13.70 [95% CI 7.82–24.31]), balance impairment (2.19 [1.09–4.16]), constipation (2.24 [2.04–2.46]), hypotension (3.23 [1.85–5.52]), erectile dysfunction (1.30 [1.11–1.51]), urinary dysfunction (1.96 [1.34–2.80]), dizziness (1.99 [1.67–2.37]), fatigue (1.56 [1.27–1.91]), depression (1.76 [1.41–2.17]) and anxiety (1.41 [1.09–1.79]) 5 years prior to diagnosis, and of tremor (7.59 [1.11–44.83]) and constipation (2.01 [1.62–2.49]) 10 years prior to diagnosis; the incidences of all prediagnostic features assessed, except neck pain or stiffness, were increased 2 years before diagnosis.

Comment: From a primary care database in the UK with large numbers of patients with PD, motor, nonmotor and autonomic features were screened for at 1, 2, 5 and 10 years prior to diagnosis. At 10 years, prior tremor and constipation were higher. At 5 years, prior tremor, impaired balance, constipation, hypotension, erectile dysfunction, urinary dysfunction, dizziness, fatigue, depression and anxiety were reported more in the group that went on to get PD. At 2 years prior, all of the prediagnostic motor and autonomic features assessed were increased (including tremor, rigidity, balance impairments, shoulder pain/stiffness, constipation, hypotension, erectile dysfunction, urinary dysfunction and dizziness) except for neck pain and stiffness, allowing the possibility of earlier detection for treatment trials and to help in an understanding of the earliest stages of different variants of parkinsonian syndromes.

Reference: Lancet Neurol 2015;14(1):57–64

Abstract

CSF biomarkers and clinical progression of Parkinson disease

Authors: Hall S et al.

Summary: This analysis of 42 patients with PD and 69 controls with baseline clinical assessment and lumbar puncture data showed that in patients with PD: i) higher baseline α-synuclein levels were associated with changes in Hoehn and Yahr score (β=0.394 [p=0.043]), UPDRS-III score (β=0.449 [p=0.013]), Timed Up and Go score (β=0.406 [p=0.023]) and A Quick Test of Cognitive Speed score (β=0.423 [p=0.018]); ii) lower baseline β-amyloid 1–42 levels were associated with worsening delayed memory recall performance (F=5.834 [p=0.022]); and iii) high phosphorylated tau levels were associated with worsening UPDRS-III scores (β=0.350 [p=0.045]) and Hoehn and Yahr scores (β=0.366 [p=0.038]).

Comment: Studies in southern Sweden on PD and controls over 2 years from baseline looking at CSF for α-synuclein, β-amyloid 1–42, tau, phosphorylated tau and neurofilaments light were compared with change in clinical characteristics that occurred over 2 years of follow-up. Higher CSF levels of α-synuclein at baseline were correlated with worsening of motor symptoms and cognitive speed over 2 years. This may reflect more intense synaptic degeneration in PD. In those with memory decline there were low CSF β-amyloid 1–42 levels, indicating greater cortical pathology.

Reference: Neurology 2015;84(1):57–63
Abstract

Improving functional disability and cognition in Parkinson disease

Authors: Peña J et al.

Summary: Forty-two patients with PD (Hoehn and Yahr stages 1–3) were randomised to 3 months of three 60-minute sessions of the REHACOP integrative cognitive training programme each week or a control group. Compared with controls, cognitive training was associated with significantly superior mean change scores for processing speed (0.13 vs. –0.15 [p=0.025]), visual memory (0.10 vs. –0.24 [p=0.011]), theory of mind (1.00 vs. –0.27 [p=0.013]) and functional disability (–5.15 vs. 0.53 [p=0.012]); the evidence in favour of cognitive training for these outcomes was categorised as class II.

Comment: In 42 persons with PD randomly assigned to cognitive retraining or standard occupational therapy activities, processing speed, visual memory, theory of mind and functional disability were all better in those who received the specific REHACOP programme. This study was for 3 months. A future study of this programme for longer would be of great interest in PD and similar neurodegenerative disorders.

Reference: Neurology 2014;83(23):2167–74
Abstract

Functional connectivity and cognitive decline over 3 years in Parkinson disease

Authors: Olde Dubbelink KTE et al.

Summary: The resting-state whole-brain and regional functional MRI (magnetic resonance imaging) scans of 55 patients with PD and 15 matched controls were reviewed in this research. Widespread decreases of resting-state functional connectivity were evident in scans from patients with PD versus controls. Comparisons with rescans from 36 patients with PD and 12 controls at 3 years follow-up showed that patients with PD had additional decreases in functional connectivity independent of aging effects, most prominently seen in posterior brain regions and correlated with clinical measures of disease progression over time, particularly cognitive decline.

Comment: Functional MRI of the whole brain in resting state was repeated at 3-year intervals and studied in relation to cognitive decline in PD. There was a progressive change in the functional connectivity in the posterior regions of the brain (characteristically affected in AD and corticobasal degeneration). The strong correlation with decreasing cognitive performance supports the pathophysiological role in the development of dementia.

Reference: Neurology 2014;83(22):2046–53
Abstract

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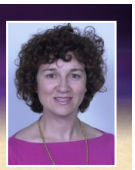

Independent commentary by Dr Karyn Boundy, FRACP

Dr Boundy is a private neurology practitioner, and is also Clinical Cognitive Research Unit/Clinical Trials Senior Visiting Neurologist at the Memory Unit/Neurology/Clinical Trials, at The Queen Elizabeth Hospital in SA, and a clinical lecturer at the University of Adelaide. She is a member of a number of neuroscience committees, and has been involved in numerous clinical trials.

Relationship between apathy and cognitive dysfunctions in *de novo* untreated Parkinson's disease

Authors: Santangelo G et al.

Summary: The association between apathy and cognitive dysfunction was prospectively evaluated in 62 patients with prodopaminergic agent-naïve PD of <2 years duration. According to S-AES (Apathy Evaluation Scale) and diagnostic criteria, apathy was present in eight participants at both baseline and follow-up, eight at baseline only and nine at follow-up only, while the remaining 37 participants were free of apathy at baseline and follow-up. All four of these subgroups of participants experienced declines in cognitive performance. Compared with participants with no apathy at baseline and follow-up, those with apathy at both baseline and follow-up performed worse on visuospatial and frontal tests, and those with apathy at follow-up but not at baseline had lower scores on the interference task of the Stroop test. A regression analysis revealed that the only independent predictor of onset of apathy at follow-up was poor baseline Stroop test interference task score.

Comment: Apathy can occur in association with depression and early stages of PD (and AD). This study was of drug-naïve PD of ≤2 years not on dopaminergic therapy. After comprehensive neuropsychological testing 2 years apart, not all PD clients had apathy, but there was an association between apathy and dysexecutive syndrome (interference task on Stroop test).

Reference: Eur J Neurol 2015;22(2):253–60
Abstract

Action tremor in Parkinson's disease: frequency and relationship to motor and non-motor signs

Authors: Gigante AF et al.

Summary: This cross-sectional study of 237 patients with PD (Hoehn and Yahr stages 1–2) reported that action tremor was seen in 46% of the patients and was associated with severity of rest tremor (adjusted odds ratio 3.0 [p<0.001]) and rigidity (1.5 [p=0.004]), but not bradykinesia or axial symptoms. Moreover, participants with versus without action tremor also had a significantly lower mean number of NMS (2.1 vs. 2.4 [p=0.04]).

Comment: Action tremor is more characteristically present in essential tremor and dystonia, but can also be seen in PD leading to early misdiagnosis or incorrect treatment. This cross-sectional study looked at NMS and motor symptoms in relation to action tremor in PD and found rest tremor and rigidity were related. How there was a lower burden of NMS? Nondopaminergic mechanisms contribute.

Reference: Eur J Neurol 2015;22(2):223–8
Abstract

Combined rasagiline and antidepressant use in Parkinson disease in the ADAGIO study: effects on nonmotor symptoms and tolerability

Authors: Smith KM et al., for the ADAGIO Investigators

Summary: This exploratory *post hoc* analysis of the ADAGIO trial, which randomised patients with *de novo* PD to receive delayed-start rasagiline 1 or 2 mg/day or placebo, examined the impact of rasagiline on depression, cognition and other NMS among 191 participants who received an antidepressant during the trial's 36-week phase 1 period. Compared with placebo, rasagiline was associated with significantly less worsening of Movement Disorder Society-UPDRS item-adjusted mean depression and cognition scores of –0.19 and –0.20 (respective p values 0.048 and <0.001), Parkinson Fatigue Scale score of –0.42 (p<0.001) and daytime sleepiness score of –0.24 (p=0.006), and a trend for less worsening of apathy scores, but no difference for anxiety and sleep scores; the effect on depression remained significant after controlling for improvement in motor symptoms.

Comment: Disease-related dopamine deficiency in early PD may contribute to depression, cognitive impairment and other NMS. The addition of the dopaminergic enhancing medication rasagiline added to an antidepressant is reported here. Adverse effects of the combination were uncommon and reduced worsening of NMS occurred. (In my personal experience, treating dopamine deficiency improves mood and cognition significantly.)

Reference: JAMA Neurol 2015;72(1):88–95
Abstract

Disease penetrance of late-onset parkinsonism

Authors: Trinh J et al.

Summary: This meta-analysis of 49 studies (n=709) compared the penetrance of mutations previously associated with late-onset parkinsonism (*SNCA*, *LRRK2*, *VPS35*, *EIF4G1* and *DNAJC13*). Significantly different age-dependent cumulative incidences were seen for all the autosomal dominant PD mutations assessed (p<0.001). In particular, *SNCA* duplication penetrance was comparable to point mutations (p=0.97) and was driven by inclusion of *SNCA* p.A53T (mean age at onset 45.9 years). Israeli Ashkenazi Jewish carriers of *LRRK2* p.G2019S were comparable to Tunisian Arab Berbers carriers (respective mean ages at onset 57.9 and 57.1 years [p=0.58]), whereas Norwegian carriers, with a mean age at onset of 63 years, differed significantly from the other groups (p<0.001).

Comment: Mutations in *SNCA*, *LRRK2*, *VPS35*, *EIF4G1* and *DNAJC13* are all genes implicated in late-onset PD. This was a meta-analysis of 49 studies and 709 persons until Jan 2014. The various mutations had different ages of onset and different ethnicities, suggesting genetic and/or environmental risk factors. The presence of modifier genes may be important in autosomal dominant PD mutations.

Reference: JAMA Neurol 2014;71(12):1535–9
Abstract

APOE, *MAPT*, and *SNCA* genes and cognitive performance in Parkinson disease

Authors: Mata IF et al.

Summary: Genotyping and cognitive impairment tests were undertaken in 1079 patients with PD. Patients with the *APOE* ε4 allele had significantly lower performance on memory tests (HVLT-R [Hopkins Verbal Learning Test – Revised] Total Recall, Delayed Recall and Recognition Discrimination Index), a semantic verbal fluency test and attention and executive function tests (Letter-Number Sequencing Test and Trail Making Test). The scores for the HVLT-R Total Recall and the semantic verbal fluency tests were lower in patients with the *APOE* ε4 allele without dementia (n=645). No significant associations were seen between *MAPT* and *SNCA* variants and any of the test scores.

Comment: In studying patients with PD from six academic centres in the US, *MAPT* and *SNCA* genes were not associated with lower scores; only *APOE* ε4 allele was associated with lower performance on total recall, delayed recall and slower verbal fluency tests and impaired Trail Making Test B. It was noted also in the control group that those with *APOE* ε4 without dementia also had lower scores.

Reference: JAMA Neurol 2014;71(11):1405–12
Abstract

Efficacy and safety of cholinesterase inhibitors and memantine in cognitive impairment in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies

Authors: Wang H-F et al.

Summary: This was a systematic review with meta-analysis and trial sequential analysis of ten trials investigating treatments for cognitive impairment or dementia due to PD and dementia with Lewy bodies. Small global efficacy on clinicians' global impression of change was seen with cholinesterase inhibitors and memantine with weighted mean differences of –0.40 to –0.65, while cholinesterase inhibitors, but not memantine, were associated with significant improvements in MMSE (Mini-Mental State Examination) cognition scores of 1.04–2.57. While good safety outcomes were generally seen with cholinesterase inhibitors and memantine, the mild-to-moderate adverse event risk was significantly greater with rivastigmine than placebo (adjusted risk ratio 1.19 [95% CI 1.04–1.36]).

Comment: Updated information on treatment for cognitive impairment or dementia due to PD and dementia with Lewy bodies from these studies showed strong benefits from cholinesterase inhibitors for cognition (MMSE), and on the global assessments both cholinesterase inhibitors and memantine. The safety profile of these drugs is well known (in AD) and there did not appear to be additional adverse events in PD, although there was a slightly greater report of adverse events with rivastigmine versus placebo. Prescription of these agents is off-label at this time in Australia, but rivastigmine patches have been used extensively elsewhere for these conditions. One of the main issues in studying PD with dementia with these agents has been identification and typing of the cognitive type.

Reference: J Neurol Neurosurg Psychiatry 2015;86(2):135–43
Abstract

Interactions between cognitive and sensory load while planning and controlling complex gait adaptations in Parkinson's disease

Authors: Pieruccini-Faria F et al.

Summary: Patients with PD and healthy controls were required to walk toward and step over an obstacle with no visual restrictions, vision of the obstacle and their lower limbs while in complete darkness and vision of the obstacle only while in complete darkness, and with and without a dual task. No significant interactions were seen between visual feedback and dual task conditions during the obstacle approach. However, compared with controls, patients with PD exhibited: i) greater deceleration and step time variability in the late phase of the obstacle approach while walking in both the darkened conditions: ii) contact with the obstacle more often when vision of their lower limbs was not available during the dual task condition; and iii) worse dual task performance only while walking in the dark regardless of visual feedback.

Comment: Trips and falls in PD often occur at the time of planning to step over an obstacle. The interaction and cognitive load required for planning to step over an obstacle requires processing of multiple visual cues (position of feet, obstacle position, step size), and places increased demand on central processing cues.

Reference: BMC Neurol 2014;14:250
Abstract

Increased risk of impulse control symptoms in Parkinson's disease with REM sleep behaviour disorder

Authors: Fantini ML et al.

Summary: Consecutive clinic patients with PD were screened for probable REM sleep behaviour disorder in this research assessing the frequency of ICDs and related behaviours; probable REM sleep behaviour disorder was identified in 106/216 patients. Compared with patients with PD without probable REM sleep behaviour disorder, those with probable REM sleep behaviour disorder had a longer PD duration, a higher Hoehn and Yahr score and a greater levodopa-equivalent daily dose, but no difference in dopamine agonist use. Patients with probable REM sleep behaviour disorder were also more likely to have ≥1 ICD or related behaviour (53% vs. 28%; adjusted relative risk 1.84 [p=0.01]), any ICD symptom only (2.59 [p=0.001]) and symptoms of pathological gambling (4.87 [p=0.049]).

Comment: Identifying those at risk of ICDs is important in avoiding pathological gambling, compulsive eating/sexual behaviours, punding and dopamine dysregulation syndrome; these are all difficult to treat and resolve. This study of 216 patients with PD identified that REM sleep behaviour disorder had a relative risk increase of 1.84 for ICD. Prior warning of this is always useful in prescribing dopaminergic drugs!!!

Reference: J Neurol Neurosurg Psychiatry 2015;86(2):174-9
Abstract

