Parkinson's Disease Research Review™

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Issue 15 – 2014

In this issue:

Welcome to the fifteenth issue of Parkinson Disease (PD) Research Review.

This issue includes research suggesting that dysfunction of the circadian melatonin rhythm could explain excessive sleepiness in PD. There is also research from the Netherlands showing that combining actigraphy with questionnaires might help diagnose REM (rapid eye movement) sleep behaviour disorder in patients with PD. Canadian researchers have shown that early mild cognitive impairment in PD is associated with faster grey matter thinning in various cortical regions and significant reductions of limbic subcortical structures. This issue concludes with research examining grey matter atrophy patterns associated with PD-related visual hallucinations.

I hope you enjoy the papers I have selected for this issue, and I am looking forward to receiving your comments, feedback and suggestions.

Kind regards,

Dr Karyn Boundy

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Skin nerve α-synuclein deposits: a biomarker for idiopathic Parkinson disease

Authors: Donadio V et al.

Summary: This research involving 21 well-characterised patients with idiopathic PD, 20 with parkinsonism assumed not to have α-synuclein deposits (comprised of ten fulfilling clinical criteria for vascular parkinsonism, six for tauopathies and four with parkin mutations) and 30 controls explored: i) the value of phosphorylated α-synuclein deposits in skin nerve fibres as a biomarker for idiopathic PD; and ii) the underlying pathogenesis of peripheral neuropathy associated with the condition. Small nerve fibre neuropathy prevalent in the leg with preserved large nerve fibres was more commonly seen among the patients with idiopathic PD, while normal large and small nerve fibres were seen in those with parkinsonism assumed not to have α-synuclein deposits. No skin samples taken from the patients assumed to not have α-synuclein deposits or controls were found to contain phosphorylated α-synuclein, but this was seen in proximal (cervical)-site skin samples from all patients with idiopathic PD. A correlation was seen between abnormal deposits and leg epidermal denervation.

Comment: This technique may provide a simple biomarker for idiopathic PD, as well as information on the pathogenesis of the neuropathy. Non-α-synuclein and vascular parkinsonism were compared with idiopathic PD. The small skin nerves had neuritic inclusion of α-synuclein, which correlated with small fibre neuropathy, suggesting a direct role in nerve injury.

Reference: Neurology 2014;82(15):1362–9

http://www.neurology.org/content/82/15/1362.abstract

Circadian melatonin rhythm and excessive daytime sleepiness in Parkinson disease

Authors: Videnovic A et al.

Summary: The relationships between the 24-hour melatonin rhythm and self-reported sleep quality, daytime sleepiness and disease metrics were explored in this cross-sectional study of 20 patients with PD receiving stable dopaminergic therapy and 15 age-matched controls. Compared with controls, the patients with PD had significantly lower amplitude of the melatonin rhythm and 24-hour melatonin AUC (area under the curve) for circulating melatonin levels ($p<0.001$), but markers of the circadian phase did not differ significantly. The amplitude of the melatonin rhythm and 24-hour melatonin AUC were also significantly lower in patients with PD who experienced excessive daytime sleepiness (Epworth Sleepiness Scale score ≥10) compared with those who did not ($p=0.001$). In patients with PD, disease duration, UPDRS (Unified Parkinson Disease Rating Scale) score, levodopa equivalent dose and global Pittsburgh Sleep Quality Index score were not significantly related to melatonin circadian rhythm measures.

Comment: Excess sleepiness and disturbances of the sleep-wake cycle are common in PD. Melatonin is a marker of the endogenous circadian rhythm. In patients with PD with an Epworth Sleepiness Scale score ≥10, over 24 hours there was a lower amplitude of melatonin secretion.

Reference: JAMA Neurol 2014;71(4):463–9
http://archneur.jamanetwork.com/article.aspx?articleid=1833933

Olfactory dysfunction in sporadic Parkinson's disease and LRRK2 carriers

Authors: Johansen KK et al.

Summary: These researchers performed neurological examinations and olfactory sense tests in 90 patients with *de novo* sporadic PD, 17 with LRRK2 PD, 36 healthy LRRK2 mutation carriers and 15 healthy family members without LRRK2 mutation. Patients with sporadic PD had significantly lower olfactory sense scores than patients with LRRK2 PD ($p<0.001$), with the lowest scores seen in patients with medicated sporadic PD and higher scores in those with *de novo* sporadic PD. Olfactory sense scores were similar between patients with LRRK2 PD and both healthy LRRK2 mutation carriers and healthy family members without mutation after adjustment for age.

Comment: Impaired smell testing maybe a preclinical marker in sporadic PD compared with other genetic forms of PD, e.g. LRRK2.

Reference: Acta Neurol Scand 2014;129(5):300–6
http://onlinelibrary.wiley.com/doi/10.1111/ane.12172/abstract

Cognitive impairment in early-stage non-demented Parkinson's disease patients

Authors: Pfeiffer HCV et al.

Summary: These researchers described cognitive profiles in 80 patients with early-stage PD and no prior clinical suspicion of cognitive impairment, depression or psychiatric disturbances; 76 underwent neuropsychological testing. Modified PD-MCI (PD-mild cognitive impairment) criteria were met by 34% of the patients, among whom 69% had evidence of episodic memory deficits, 54% executive dysfunction, 50% language/praxis deficits, 46% visuospatial/constructional deficits and 35% attention/working memory deficits. Associations were seen between cognitive impairment and higher UPDRS, bradykinesia and rigidity scores and a more symmetric distribution of symptoms, but not tremor scores. Patients with and without cognitive impairment had comparable demographic and clinical variables, with the exception of education level, which was lower among those with cognitive impairment.

Comment: Mild cognitive impairment in early-stage PD is common. Early PD sufferers had episodic memory deficits (69%), executive dysfunction (54%), language/praxis dysfunction (50%), visuospatial deficits (46%) and attention and working memory deficits (35%). These appeared to be more prominent with greater bradykinesia, rigidity and axial symmetrical symptoms relevant to the akinetic forms of parkinsonism.

Reference: Acta Neurol Scand 2014;129(5):307–18
http://tinyurl.com/lc3294v

Actigraphy as a diagnostic aid for REM sleep behavior disorder in Parkinson's disease

Authors: Louter M et al.

Summary: The utility of eight consecutive nights of actigraphy for diagnosing REM sleep behaviour disorder was investigated in 45 consecutive patients with PD. Compared with participants without REM sleep behaviour disorder, those who met the ICSD-II (International Classification of Sleep Disorders) criteria for the condition (n=23) had a significantly higher total number of wake bouts (73.2 vs. 48.4 [p=0.016]). Using a cutoff of 95 wake bouts per night, actigraphy diagnosed REM sleep behaviour disorder with specificity of 95.5%, sensitivity of 20.1% and a positive predictive value of 85.7%. Among participants with suspected REM sleep behaviour disorder based on an interview alone but not confirmed on video polysomnography (n=7), six had <95 wake bouts per night on actigraphy.

Comment: Actigraphy is a noninvasive method of monitoring sleep activity via monitoring gross motor activity, and it can detect daytime sleepiness, insomnia, circadian rhythm disturbances, restless legs, etc. This may, in conjunction with REM sleep behaviour questionnaires, be a promising method for diagnosing REM sleep behaviour disorder in PD.

Reference: BMC Neurol 2014;14:76
http://www.biomedcentral.com/1471-2377/14/76

Environmental neurotoxic challenge of conditional alpha-synuclein transgenic mice predicts a dopaminergic olfactory-striatal interplay in early PD

Authors: Nuber S et al.

Summary: To investigate the potential role of olfactory α-synuclein accumulation in the pathogenesis of early PD, these researchers administered low doses of paraquat (a herbicide) to mice with site-specific and inducible overexpression of familial PD-linked mutant α-synuclein in olfactory bulb neurons. They found that: i) olfactory α-synuclein *per se* elicited structural and behavioural abnormalities that were characteristic of an early timepoint in models with widespread α-synuclein expression, including increased striatal dopaminergic marker and hyperactivity; ii) α-synuclein suppression reversed the dopaminergic phenotype; and iii) paraquat synergistically induced olfactory dopaminergic cell degeneration and opposed the higher reactive phenotype. Mice with suppressed α-synuclein expression that were treated with paraquat did not exhibit neurodegeneration or behavioural abnormalities. Paraquat induced a pathological cascade, via increased calpain activity, that resulted in inhibition of autophagy clearance and accumulation of calpain-cleaved truncated and insoluble α-synuclein, which recapitulate the biochemical and structural changes seen in PD in humans.

Comment: There is an increased incidence in some population groups of PD (e.g. farmers) that could potentially relate to the finding of this study, i.e. increased vulnerability of olfactory neurons to neurotoxins in the presence of α-synuclein pathology.

Reference: Acta Neuropathol 2014;127(4):477–94
http://link.springer.com/article/10.1007/s00401-014-1255-5

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Independent commentary by Dr Karyn Boundy, FRACP

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Mild cognitive impairment is linked with faster rate of cortical thinning in patients with Parkinson's disease longitudinally

Authors: Hanganu A et al.

Summary: Longitudinal changes of cortical and subcortical grey matter were investigated in patients with PD with and without mild cognitive impairment and healthy controls. Compared with cognitively stable patients and healthy controls, patients with PD with mild cognitive impairment had greater cortical thinning rates in the temporal, occipital, parietal and supplementary motor areas, while cognitively stable patients with PD had increased thinning rates involving only one lateral occipital and one fusiform cluster compared with healthy controls. Significant thinning in similar regions, including the temporal and medial occipital lobes, was associated with cognitive decline across all patients. Patients with PD with mild cognitive impairment also had significant lower amygdala and nucleus accumbens volumes.

Comment: Predicting who may decline cognitively in PD (a similar situation to Alzheimer disease) may be important, as disease-modifying antisynuclein therapies might become available. Persons with more significant rates of change of cortical thickness, especially in the temporal and medial occipital lobes, appear to be more susceptible to dementia.

Reference: Brain 2014;137(4):1120–9
http://brain.oxfordjournals.org/content/137/4/1120.abstract

Selective serotonin reuptake inhibition modulates response inhibition in Parkinson's disease

Authors: Ye Z et al.

Summary: This study randomised 21 patients with idiopathic PD to receive citalopram 30mg or placebo added to their usual dopaminergic medication in two separate sessions, with 20 matched unmedicated healthy control subjects also evaluated. Compared with controls, placebo recipients had longer Stop-Signal reaction times and more NoGo errors, confirming that PD causes impairment in response inhibition, and this was associated with less stop-specific activation in the right inferior frontal cortex, but no significant difference for NoGo-related activation. No beneficial main effect of citalopram was seen, but it was associated with a reduction in Stop-Signal reaction time and NoGo errors, and enhanced inferior frontal activation, in participants with relatively higher UPDRS motor scores. Correlations were evident between the behavioural effect and citalopram-induced prefrontal activation enhancement and the strength of preserved structural frontostriatal connectivity.

Comment: Impaired response inhibition, i.e. impulsivity, is common in PD due to structural changes in the frontostriatal circuits and dopaminergic overdose. This symptom may respond to citalopram (which enhances prefrontal activation); however, as PD progresses, there is progressive loss of forebrain serotonergic neurons.

Reference: Brain 2014;137(4):1145–55
http://brain.oxfordjournals.org/content/137/4/1145.full

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Reduced glucocerebrosidase is associated with increased α-synuclein in sporadic Parkinson's disease

Authors: Murphy KE et al.

Summary: The relationships between PD-specific glucocerebrosidase deficits, glucocerebrosidase-related pathways and α-synuclein levels were explored using autopsy brain tissue samples from 19 patients with sporadic PD without GBA1 mutations and ten *post mortem* delay-matched controls. Selective reductions in glucocerebrosidase protein levels and enzyme activity were seen in early-stage PD in regions with increased α-synuclein levels but limited inclusion formation, while nonselective reductions were seen for GBA1 messenger RNA expression in PD. Direct relationships were seen between the selective lysosomal glucocerebrosidase loss and reduced lysosomal chaperone-mediated autophagy, increased α-synuclein and decreased ceramide.

Comment: The heterozygous mutation GBA1 gene for lysosomal cerebrosidase is the most frequent known genetic risk for PD. This paper looking at non-GBA1 sporadic PD found that there were selectively reduced glucocerebrosidase protein levels and enzyme activity in early PD in the regions where α-synuclein accumulated. This suggests cellular membrane/lysosomal function is reduced in regions vulnerable to PD pathology.

Reference: Brain 2014;137(3):834–48
http://brain.oxfordjournals.org/content/137/3/834.abstract

Visuoperceptive region atrophy independent of cognitive status in patients with Parkinson's disease with hallucinations

Authors: Goldman JG et al.

Summary: Using structural MRI (magnetic resonance imaging), these researchers examined grey matter atrophy patterns associated with visual hallucinations in 25 patients with PD-associated current and chronic visual hallucinations and 25 patients with PD without hallucinations matched for cognitive status and age. Compared with the patients without visual hallucinations, all those who experienced hallucinations had grey matter atrophy with significant voxel-wise differences in the cuneus, lingual and fusiform gyri, middle occipital lobe, inferior parietal lobule, and cingulate, paracentral and precentral gyri. The grey matter atrophy in patients was predominantly located in the brain regions responsible for processing visuoperceptual information, including the ventral 'what' and dorsal 'where' pathways. In addition, the structural brain changes seen on MRI were not dependent on cognitive function or age.

Comment: The predominance of visual only hallucinations in PD is likely due to malfunction/atrophy of visuospatial pathways (rather than the medial temporal lobe). There may be distinct MRI structural differences in those with hallucinations.

Reference: Brain 2014;137(3):849–59
http://brain.oxfordjournals.org/content/137/3/849.abstract

