Extending our Understanding of the Dopaminergic Basis of Non-motor Symptoms in Parkinson's Disease

Highlights of a Britannia symposium held at the 10th International Congress on Non-Motor Dysfunctions in Parkinson's Disease and Related Disorders, 5th December 2014, Nice, France

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Abstract

Parkinson's disease (PD) is primarily considered as a motor disorder but there is increasing recognition of the wide range of non-motor symptoms (NMS), such as low mood, pain, apathy, fatigue and sleep problems, which may be experienced by PD patients across the spectrum of the disease. Notably, NMS often occur before motor symptoms develop and are known to place a significant burden on health-related quality of life (HRQoL) of the person with PD. Commonly, NMS go undiagnosed by the clinician and are therefore undertreated; however, to optimise patient outcomes, both motor and non-motor aspects of PD need to be recognised and managed effectively. The 10th International Congress on Non-Motor Dysfunctions in Parkinson's Disease and Related Disorders held in Nice, France, in December 2014, offered the opportunity to look further into the dopaminergic basis of NMS and how this may affect clinical management. Britannia arranged an international faculty, chaired by Professor Amos Korczyn (Tel Aviv, Israel), to review the latest developments in our understanding of the underlying aetiology and clinical burden of non-motor features in PD that will ultimately help inform clinical practice. Surveys indicate that NMS have an extremely high prevalence among PD patients and evidence now suggests that it is the total 'burden' of NMS, combining frequency and severity, and not just the occurrence of individual NMS such as depression, which is the major determinant of a patient's HRQoL. Recognising the significant contribution of NMS to the total clinical picture in PD, in order to provide a more comprehensive grading of PD severity, it is now proposed that the clinical assessment of PD patients needs a combined approach using for example the validated Non-motor Symptoms Scale (NMSS) to assess total NMS burden in addition to classic motor symptom scoring. Recent data from newly diagnosed PD patients also suggests there are different subtypes of PD that may have implications for both clinical trial design and the selection of therapy. Cognitive impairment often occurs in patients with PD, even in early disease, progressing to PD dementia in a substantial proportion of patients, which can limit therapeutic options. Posterior cortical dysfunction is a negative predictor of the progression of PD with mild cognitive impairment to PD dementia. Pronounced nigrostriatal denervation is characteristic of PD; however, cholinergic changes are also observed. Cholinergic depletion starts early in the disease process and by the time PD dementia develops patients will have a significant cholinergic deficit in various cortical regions. Current research is focused on the potential to reduce cognitive decline by decreasing beta-amyloid plaques.

Keywords

Parkinson's disease (PD), non-motor symptoms, dopamine, cognitive impairment, apomorphine

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Non-motor Symptoms in Parkinson's Disease – Impact, Recognition and Management

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Professor Chaudhuri considered that non-motor symptoms (NMS) were an integral part of Parkinson's disease (PD) and the leading cause of poor quality of life (QoL) in PD patients. The association of NMS with motor PD has been recognised since the disease was first identified – in his original essay on PD, James Parkinson described several non-motor issues, including sleepiness and autonomic dysfunction.[1] NMS often pre-date motor symptoms by 10–15 years[2–4] and research on this topic has revealed that late onset hyposmia and rapid eye movement sleep disorder are possible pre-motor markers of motor PD.[5] In terms of the patient experience, evidence now suggests that it is the total 'burden' of NMS, not just the occurrence of individual NMS such as depression, that is the major determinant of health-related QoL (HRQoL) in PD patients.[6] In the Sydney multicentre study, long-term follow-up of PD patients for 20 years found that they were often troubled to a greater extent by NMS than by motor symptoms.[7] As a result, PD is now considered by some to be a neuropsychiatric disorder.

NMS are highly prevalent in PD patients and several studies have reported that almost all patients (>98 %) report some symptoms.[3,8] Data accumulated from eight international studies including over 2,500 PD patients indicate that most PD patients will report at least eight different NMS when assessed using the validated Non-Motor Symptoms Questionnaire: NMSQuest.[9]

An evolving area of research in PD relates to different genetic forms of PD and how they relate to non-motor signs. At least 18 mutations in the synuclein alpha (*SNCA*) gene, one of the *PARK* family of genes known to be associated with PD, have been described. Analysis of SNCA mis-sense mutations and multiplications, albeit in a relatively small number of PD patients, has suggested that dementia is a marker for this genetic form of PD.[10] *LRRK2* (leucine-rich repeat kinase 2, another of the *PARK* gene family) mutations on the other hand are commonly associated with sleep disorders. *LRRK2* mutation carriers often have a marked degree of insomnia, including disturbed sleep patterns with repeated wakening, a troubling form of restless leg syndrome and a high frequency of early morning 'off' periods. Variations in the *GBA* (glucosidase beta acid) gene are commonly seen in PD and parkinsonism. *GBA* mutations seem to be associated with autonomic issues, dementia and hallucinations, and patients often have a high degree of anxiety and depression. These emerging data on the non-motor markers of genetic subtypes of PD may help refine treatment strategies in the future.

Advances in our understanding of PD has prompted a review and redefinition of the disease led by the Movement Disorder Society (MDS) Task Force on the Definition of PD.[11,12] The work is ongoing and likely to develop further in the future. Three phases of the disease are recognised and notably NMS appear earlier than motor manifestations in the disease process:

- Preclinical PD: PD-specific pathology is assumed to be present, supported by molecular or imaging markers, but there are not clinical signs or symptoms of PD.
- Premotor PD: Characterised by the presence of early non-motor signs and symptoms due to extranigral PD pathology.
- Motor PD: PD pathology involves the substantia nigra leading to nigrostriatal dopamine deficiency that causes motor manifestations followed by later non-motor features.

Table 1: Classification of Patients by Hoehn and Yahr Stage and Non-motor Symptom Burden Levels Showing a Weak Correlation Between the Two Scales[8]

Hoehn and Yahr Stages	Non-motor Burden Levels					Total
	0	1	2	3	4	
1	3	55	38	19	9	124
2	2	126	122	87	67	404
3	0	55	56	81	88	280
4	0	7	16	29	54	106
5	0	0	1	2	16	19
Total	5	243	233	218	234	933

Goodman and Kruskal's gamma = 0.45; asymptotic standard error (ASE) = 0.032. Reproduced with permission from PLoS One.

As mentioned previously, NMS are a recognised driver of HRQoL in PD patients. There is now a substantial amount of data confirming a correlation between the occurrence of NMS and poor QoL scores, assessed using the Parkinson's Disease Questionnaire (PDQ)-39 instrument.[3,13] In a multicentre, international, cross-sectional study of 411 PD patients, using a multiple linear regression model, Martinez-Martin and colleagues also demonstrated that HRQoL correlates most closely with the overall the burden of NMS.[6] In this study, the Non-motor Symptoms Scale (NMSS) was used to determine the prevalence of NMS along with clinical (Hoehn and Yahr [H&Y] staging and SCOPA-Motor Scale [S-MS]) and HRQoL measures (PDQ-39 and EQ-5D). NMSS is a validated scale that allows clinicians to quantify the frequency and severity (burden) of NMS in the clinic. The total NMSS score showed a higher correlation coefficient (Spearman r=0.70) with the PDQ-39 Summary Index (SI) than with S-MS (r=0.58) and was the best predictor of HRQoL, as measured by the PDQ-39 SI.

It has recently been proposed that NMSS scores should be used to determine different levels of NMS burden (NMSB) in PD patients that, when combined with standard motor symptom scoring, could provide a more comprehensive grading of PD severity than is currently achieved with routine assessment.[8] In this study of 951 PD patients, NMSB levels were assigned as mild (1), moderate (2), severe (3) or very severe (4) according to the NMSS score range of (1) 1–20, (2) 21–40, (3) 41–70 and (4) ≥71. Increasing PDQ-8 Index scores, indicating reduced QoL, correlated with higher NMSB levels. By contrast, there was poor correlation between NMSB levels and H&Y stage – some patients with early stage PD (H&Y stage 1) had high NMSB levels, illustrating that motor severity in PD does not go hand-in-hand with non-motor burden (see *Table 1*).

Although previously considered as primarily a disease associated with dopamine depletion, it is now recognised that multiple pathways – noradrenergic, serotonergic and cholinergic – are also involved in its pathology.[14] In addition, the variability in the clinical phenotype of PD suggests the existence of several subtypes of the disease. This hypothesis was investigated in a large cohort of newly diagnosed, untreated PD patients.[15] Data were collected on demographics, motor symptoms and NMS from 100 subjects and a cluster analysis performed that allowed the identification of different subgroups of PD patients. Four distinct groups were identified that could be classified as (1) benign pure motor, (2) benign mixed motor–non-motor, (3) non-motor dominant and (4) motor dominant. Other investigations of some of the clinical and pathological features of PD provide further evidence that PD is more than just a loss of mid-brain dopaminergic neurons in association with Lewy bodies.[16] Halliday and colleagues have shown that early-onset PD neurodegeneration and Lewy body deposition (predominantly limbic involvement) is different from that seen in later-onset disease (predominantly cortical and superior brainstem involvement). This leads to segregation into three distinct endophenotypes: brainstem dominant, limbic dominant and cortical dominant, each associated with different clinical signs. Brainstem dominant is mostly associated with sleep symptoms and dysautonomia, limbic dominant with symptoms of fatigue and pain and cortical dominant with cognitive symptoms and apathy. Emerging literature suggests these phenotypes can also be observed in untreated PD patients. The recognition of different PD subtypes and how they respond to therapy has important implications for the conduct of clinical trials and in the future is likely to influence the selection of the most suitable treatment for individual PD patients. ■

Cognitive Decline in Parkinson's Disease – Research Developments

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Professor van Laar emphasised the considerable differences between the development of motor symptoms throughout the course of PD and the development of NMS and cognitive deterioration. A recent study has investigated the rate and pattern of progression of cognitive deficits in aged and long-lasting non-demented PD patients.[17] A total of 49 non-demented patients, 23 cognitively normal (PD-CN) and 26 with mild cognitive impairment (PD-MCI) were studied over 31 months using individual tests over cognitive domains. All patients were at least 60 years old and had had PD for 10 years or more. The results found that 21.7 % of PD-CN patients progressed to MCI and 42.3 % of PD-MCI patients progressed to dementia over the observation period. The transition from cognitively normal to MCI was characterised by attention, executive and memory dysfunction and the evolution from MCI to dementia was marked by the appearance of visuospatial deficits and worsening of attention and executive function. This suggests that posterior-located cortical functions drive the conversion from PD-MCI to dementia.

A population-based study has recently reported 10-year follow-up data evaluating the natural history of incident PD, including its progression to dementia, significant motor disability (Hoehn and Yahr stage 3 and mortality), with the aim of identifying predictors of outcome.[18] The study found that within 5 years, about 50 % of patients developed postural instability and this seemed to precede cognitive deterioration. At 10 years 46 % had developed dementia.

The different stages in the progression of synucleinopathy in PD, from the pre-symptomatic through to the symptomatic phase, according to the hypothesis of Braak and colleagues, are now well recognised.[19] Less well known is another pathological event observed during cognitive decline in PD patients, namely amyloid deposition. A cross-sectional study was undertaken to examine the relationship between corticostriatal beta-amyloid deposition and cognitive dysfunction in a cohort of 40 patients with PD who had MCI or other known dementia risk factors.[20] Subjects underwent beta-amyloid and vesicular monoamine transporter 2 positron emission tomography (PET) imaging using the 11C-Pittsburgh compound B (PiB) tracer and neuropsychological assessment. The results showed that only six of the 40 subjects (15 %) showed elevated PiB binding at levels usually seen in patients with Alzheimer's disease. Of these six patients, four had PD dementia and two had PD-MCI.

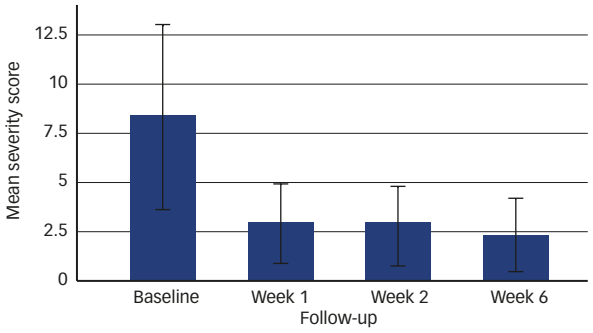
Postural instability and gait difficulty (PIGD) features are known to be risk factors for the development of PD dementia. To investigate this relationship, a cross-sectional PET study was undertaken to examine neocortical beta-amyloid deposition and PIGD feature severity in 44 PD patients who were at risk of dementia.[21] Linear regression analysis showed that increased PIGD feature severity was associated with increased neocortical PiB binding.

Investigation of neurotransmitters involved in cognitive decline in PD is the focus of much research. While pronounced nigrostriatal denervation is characteristic of PD, cholinergic changes are less marked. A study by Bohnen and colleagues found that cholinergic denervation in PD patients was heterogeneous with reduced neocortical and/or thalamic acetylcholinesterase activity being observed in 36 % of non-demented PD subjects. In total, 13 % of patients were found to have both reduced neocortical and reduced thalamic acetylcholinesterase. Results of this study also showed independent cognitive effects for both cholinergic and dopaminergic system changes in these subjects. Overall, one in every three non-demented PD patients in the study had developed significant cholinergic deficit.

PET imaging studies using the tracer MP4A have been performed to evaluate cholinergic and dopaminergic transmitter changes in 17 non-demented patients with PD and 10 patients with PD dementia.[22] Cortical MP4A binding was severely reduced in patients with PD dementia (29.7 %, $p<0.001$ versus controls) and moderately decreased in PD (10.7 %, $p<0.01$ versus controls). The PD dementia group had lower parietal MP4A uptake rates than patients with PD. So, while non-demented patients with PD had moderate cholinergic dysfunction, subjects with PD dementia were found to have significant cholinergic deficit in various cortical regions.

Olfactory dysfunction is common in people with PD but its pathophysiology and correlation with neurotransmitter deficit is poorly understood. Bohnen et al. investigated the relationship between performance on an odour identification task and forebrain cholinergic denervation in 58 PD

Figure 1: Mean (±95 % Confidence Interval) Neuropsychiatric Inventory Severity Scores in Parkinson's Disease Patients*[27]



**Patients with cognitive dysfunction and/or pre-existing visual hallucinations treated with subcutaneous apomorphine infusion. Reproduced with permission from* Parkinsonism and Related Disorders.

subjects without dementia.[23] Results showed that odour identification test scores correlated positively with acetylcholinesterase activity in the hippocampal formation, amygdala and neocortex. There was however no clear association with striatal dopaminergic deficits. These results indicate that cholinergic denervation occurs early in the course of PD and that depletion in the limbic archicortex correlates more closely with olfactory dysfunction than nigrostriatal dopaminergic denervation in subjects with moderately severe PD. This suggests that larger deficits in odour identification may signal PD patients who are at greater risk of developing clinically significant cognitive impairment.

Similar results have been observed for another common pre-motor symptom in PD: rapid eye movement sleep behaviour disorder (RBD). As with other symptoms, its specific relationship to neurotransmitter deficits of PD is presently unknown. A PET imaging study was therefore undertaken to assess the association between cholinergic denervation and symptoms of RBD in 80 PD patients without dementia.[24] The presence of RBD symptoms was found to be associated with neocortical, limbic cortical and thalamic cholinergic denervation but not with serotonergic or nigrostriatal dopaminergic denervation. Thus the authors concluded that the presence of RBD symptoms in PD subjects might be an early indicator of cholinergic system degeneration.

The risk factors for the development of dementia in PD have also been investigated. A prospective, community-based study assessed the temporal relationship between changes in predominant motor symptoms and development of dementia 171 non-demented PD patients.[25] Transition from tremor-dominant (TD) PD to the PIGD subtype was associated with a more than threefold increase in the rate of cognitive decline (assessed using the Mini-Mental State Examination [MMSE]). Compared with patients with persistent TD disease or indeterminate subtype, patients who transitioned from the TD or indeterminate subtype to the PIGD subtype had a 57-fold higher risk of developing dementia (odds ratio 56.7; p=0.003). This rose to an 80-fold higher risk (odds ratio 80.0; p=0.003) for patients with a persistent PIGD subtype and raises the question of whether PIGD and dementia share a common pathology.

The CamPaIGN study is a longitudinal, long-term study investigating the development of cognitive impairment and dementia in a population-representative cohort of 126 PD patients.[26] Initial investigations identified three predictors of dementia risk, namely, age ≥72 years, semantic fluency of fewer than 20 words in 90 seconds and the inability to copy an intersecting pentagons figure, which could be easily used in the clinic. The MAPT H1/H1 genotype was also found to be an important risk factor. Ten-year follow-up data from the study have also identified additional predictors of outcome.[18] Predictors of a poor outcome, and an increasing chance of conversion to MCI or PD dementia, were age, high unified Parkinson's disease rating scale (UPDRS) motor score, high Beck depression score and the presence of comorbidities. Predictors of a good outcome (surviving free of dementia/postural instability) were TD motor phenotype, good MMSE scores and semantic fluency.

It is a commonly held belief that dopamine agonists should not be given to PD patients who have cognitive impairment; however, Professor van Laar described a study undertaken by his own research group investigating the use of continuous subcutaneous apomorphine infusion in PD patients with cognitive dysfunction and/or pre-existing visual hallucinations.[27] Patients were prescribed apomorphine to manage persistent motor response fluctuations despite existing oral medication. Neuropsychiatric inventory severity scores in this study were reduced compared with baseline at weeks 1, 2 and 6, primarily due to the reduction in visual hallucinations (see *Figure 1*). Investigation of the mechanisms underlying the effect of apomorphine on visual hallucinations found that apomorphine increased contrast sensitivity, an important factor in visual perception. This may be due to its lack of effect on D3 receptors; however, the mechanism is uncertain. Preliminary research suggests that apomorphine may also have a modifying effect on amyloid deposition in non-demented PD subjects.[28]

Brain atrophy has also been investigated as a potential biomarker of cognitive decline. Magnetic resonance imaging of the brains of 84 PD patients (61 PD with normal cognition; 12 PD-MCI; 11 PD dementia) and 23 healthy control subjects found no abnormalities PD subjects with normal cognition, hippocampal atrophy in subjects with PD-MCI, and both hippocampal and medial temporal atrophy in those with PD dementia.[29] These results confirm that hippocampal atrophy is a biomarker of initial cognitive decline in PD. Marked grey matter atrophy has also been observed in patients with PD dementia with less extensive changes in those with PD-MCI.[30] Some grey matter atrophy seems to precede the development of dementia but may accelerate once dementia begins.

When considering therapy in PD patients with cognitive decline who are likely to have cholinergic defects, a common question that arises is when should treatment with cholinesterase inhibitors (ChEIs) begin, particularly as the cholinergic depletion seems to start early in the disease course? The ChEI rivastigmine is indicated for the treatment of PD dementia but there are limited available options for earlier cognitive decline and PD-MCI. A placebo-controlled, early treatment study – the DUPRAC trial – evaluating the use of rivastigmine for the treatment of PD-MCI is currently ongoing to evaluate this. ■

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