

*Report of the*

*Fourth meeting of the UK PD Non Motor Group:*

*Non- Motor symptoms of PD: What's new?*

The fourth annual meeting of the UK Parkinson's Disease Non-Motor Group (PDNMG) was the largest yet, with over 200 delegates attending at the Royal Society of Medicine, London. This in part reflects the continued and increased recognition of Parkinson's Disease (PD) as a non-motor disease as much as a motor one.

After a brief introduction by PDNMG Chairman and Meeting Organizer, Professor K R Chaudhuri (UK), all delegates attended lectures on Olfaction and Sleep in PD (H Reichmann, Germany) and Imaging of NMS in PD (D Brooks, UK).

Bilateral and invariable olfaction is now a recognised very early NMS, and occurs in 70-100% of all PD patients independent of medication. There are significant international variations in diagnostic point after the first motor symptom, ranging from just 9 months in Japan to 15 months in France. Earlier diagnosis based on olfactory symptoms, may be pivotal to treatment choice and prognosis.

Parenchymal sonography of the Substantia Nigra (SN) along with Beta-CIT SPECT imaging has shown early idiopathic olfactory dysfunction coinciding with PD. More so, people identified as suffering from olfactory dysfunction are five times as likely to subsequently develop PD within 4 years, compared to normosmic individuals.

Whilst the motor complex of PD has long been associated with dopamine deficiency within the SN, Professor Brooks questioned the direct impact of this hormone on the gamut of NMS.

Although it appears that dopamine modulates executive function and sleep, there is no correlation between striatal dopamine and fatigue symptoms. Instead, decreased concentrations in the right insular and ventral thalamic connections are correlated with fatigue. Dementia is associated with decreased parietotemporal metabolism, as well as decreased frontal lobe dopamine storage and cortical cholinergic function. The loss of dopamine outside the nigrostriatal area defines the difference between Parkinson's Disease with Dementia (PDD) and PD. However, although decrease serotonin is seen in PD with depression, Professor Brooks suggested that this symptom is in fact reflective of noradrenaline and limbic dopamine concentrations. It may explain the success of Levodopa in treating depression, compared to antidepressants.

Cardiac MIBG scans, imaging the sympathetic nervous system, has shown a post-ganglionic deficiency in patients with PD. Recent evidence suggests that Cardiac MIBG scans of patients with RBD shows the same pattern of autonomic dysfunction, further substantiating RBD as a pre-motor NMS in PD. This is reflected by reduced uptake seen on DAT and PET imaging in RBD patients, in the same pattern as with patients with PD alone.

The next lectures, given by P Jenner (UK) and A Schapira (UK), looked at non-dopaminergic therapies in PD, and the question of when to start treatment of PD, respectively.

Use of non-dopaminergic treatments to treat PD is widespread. The wide range of transmitters and brain areas altered in PD, in addition to nigrocentric, dopaminergic systems, emphasises the importance of taking a global approach to management. However, the development in more efficacious therapies is slow, e.g. Sarizotan (5HT-agonist), and not reflective of success in animal models. Perampanel, an AMPA-type glutamate receptor antagonist, has also failed due to the ubiquity of glutamatergic receptors throughout the brain. Similarly, there has been little real progress in treating NMS in PD as a group, with clinicians still having to address each symptom individually.

'When' to treat is as perplexing a question as 'how'. Due to the heterogeneity of PD, presymptomatic time is variable, and clues to diagnosis, whether clinical, pathological, imaging based or genetic, are crude estimates. The long 'pre-symptomatic' period, where there is evidence of dopaminergic and nigrostriatal cell degeneration without motor symptoms, must be exploited. To explain this, Professor Schapira supported the theory of compensation – other parts of the brain compensate and therefore correct early basal ganglia abnormality as a means of support.

Treatment of PD appears to have short-term side effects and long term complications. However, evidence based reappraisal appears to recommend early symptomatic relief and improved quality of life, despite the inevitable undesirable effects of treatment, such as wearing off. Treatment-naive patients have lower quality-of-life scores than those receiving treatment, and early intervention should become common practice. More so, recent evidence from DATATOP, ELLDOPA, ADAGIO, and TEMPO studies even suggest better outcomes, perhaps due to a neuroprotective mechanism, for PD patients started on early treatment.

The morning's second session focused on the issue on sleepiness and parasomnias in PD. Excessive Daytime Sleepiness (EDS) is a frequent and disabling NMS of PD. It can be a result of lesions in arousal systems causing abnormal night time sleep, or as a side effect of dopaminergic treatment. Patients taking dopamine agonists are three times as likely to suffer from EDS than those on Levodopa alone. Dopamine related sleepiness occurs most often at the peak of dopamine serum concentration. However, there is only weak evidence that prolonged-release dopaminergic treatment is less sedative.

Dr I Arnulf (France) reviewed promising data on sodium oxybutyrate, an anti-narcoleptic. Small trials have shown significant decreases in Epworth Sleepiness Scale scores in patients with PD and EDS. Phase II trial data has also recently shown histamine-3 receptor antagonists to reduce EDS and motor symptoms.

Dr G Trenkwalder (Germany) demonstrated the difficulty of diagnosing RBD. Although caregiver history is essential, objective evidence from polysomnography is the gold-standard device for confirming RBD. Video of the patient during sleep is also a useful tool. RBD can change the motor-pattern during sleep, compared to daytime movements. It is also typical for vocalisation to be combined with motor acting, often in the extremities.

An individual with idiopathic RBD has a higher risk of LBD or PD. Dr Trenkwalder suggested that a flip-flop switch, which normally controls the onset of REM-Sleep, is dysregulated in PD. Lesions in the mesopontine tegmentum may sharpen state transitions, and cause the RBD phenotype.

Despite its debilitating effects on the quality of life of patient and carer, there is a deficiency of clinical trials looking at the treatment of RBD. Dr Trenkwalder echoed widespread recommendations of clonazepam or melatonin, and called for controlled trials comparing treatment strategies.

The final speaker of the session, Dr C Fowler (UK), discussed bladder dysfunction in PD. These patients are notoriously difficult to treat, and often present with advanced PD, with the associated motor side effects, high levels of disability, and speech difficulties. It is essential that any treatable urological cause of bladder dysfunction is first excluded. When choosing an acetylcholine inhibitors or anti-muscarinic medication, Dr Fowler stressed the importance of selecting those that do not affect central M1 receptors and do not cross the blood-brain barrier. Also, botulinum injection directly into the bladder wall is an exciting new treatment that can prevent hyper-reflexia, urgency and overactivity.

The format then changed for a series of 'snapshot reviews'. Professor K R Chaudhuri highlighted the need for more research into visual dysfunction in PD. The full range of visual problems may be seen in patients, ranging from retinal defects leading to contrast sensitivity or diminished blue-green colour vision, to motor defects presenting as diplopia, hypometria or dyskinesias. These NMS may be again part of a pre-motor complex, and may be best recognised using the Farnsworth-Munsell 100 Hue Test. There is a paucity of evidence that suggests that colour discrimination in PD patients is improved after ingesting levodopa.

Professor T Renton then briefly evaluated trigeminal pain in PD. Pain appears to be both prodromal and prognostic. Oculofacial pain (OFP) is extremely debilitating, and is associated with headaches, burning mouth syndrome, temporomandibular joint pain, and compromised trigeminal reflexes. Research currently being conducted by Prof Renton hopes to better identify the aetiology of OFP in PD.

The afternoon's lectures took on a new format once more, with delegates splitting into three symposia addressing therapy in advanced disease, psychiatric issues and dopamine agonists, and co-morbidities and quality of life in PD.

It is evident that Duodopa has a strong effect on motor function, with patients seeing a 70%-90% reduction in off-time, and reduced dyskinesia. More so, unpublished data suggests that pump therapies reduce NMS by 55%, particularly improving perception, and alleviating urinary dysfunction and depression.

Deep brain stimulation (DBS) also improves motor symptoms and quality of life, although its effects on NMS are less well-defined. Future treatment choice between duodopa and DBS can only be decided if and when trials directly compare them.

It was agreed that Apomorphine continues to play a role in treating late PD, albeit as a temporary solution before duodopa or DBS. Duodopa may be prohibitively expensive whilst there are significant limitations on the eligibility of patients to DBS. The debate, therefore, continues.

Psychiatric issues, particularly depression and compulsive behaviour, dominated discussion in the second symposium. Although there is clear link between serum serotonin levels in patients with PD and depression, a clinical correlation is yet to be established, with clinical studies thus far focusing more on noradrenaline abnormalities in the Locus Coeruleus. Few studies, of limited quality, are currently available comparing outcomes from using anti-depressants to dopaminergic therapy. Tricyclic antidepressants appear to be more effective than SSRIs, whilst pergolide is more effective than pramipexole. The symposium proposed a treatment algorithm to systematically treat depression. It was recommended to use dopaminergic therapy as a first line, in increasing concentrations, before considering tricyclics (despite their side effects).

The third and final symposium reviewed new developments in determining comorbidities of PD and their effects on health-related quality of life (HRQoL). Trials currently underway may provide a solution

to constipation using botulinum toxin. The importance of checking the mouth for signs of oral infection, to prevent aspiration pneumonia, was emphasised for patients with drooling and swallowing difficulties. The symposium condemned the use of current over-the-counter treatments for drooling, including various chewing gums and nutmeg-based antidotes, for which there is no evidence base. Finally, Prof Martinez-Martin (Spain) reiterated the need for more longitudinal studies on PD-HRQoL. Physicians should be acutely aware of the difference between symptoms that are determinants of HRQoL and those that dominate the clinical picture. The problems that are therefore most relevant to the patient can be identified, and the treatment pathway guided appropriately.

The first plenary speaker, N Giladi (Israel), brought a fresh perspective to the Meeting. The recent National Parkinson's Foundation opinion meeting agreed that depression and anxiety, cognitive disturbances, and immobility and falls, are the most important features of PD from a patient's perspective. Dr Giladi was keen to note that just one of these is motor, further emphasising the redefinition of PD.

Volition, planning and cognitive inhibition define executive function in successful, normal gait. PD patients who must stop walking to talk exhibit a lack of cognitive reserve. When PD patients attempt to do both simultaneously, there is an increased stride-to-stride variability and decreased speed, in direct proportion to the difficulty of the cognitive challenge.

Similarly, predictive features of falls in PD patients are dopamine agonist treatment, power of attention, and reaction time variability. Freezing of gait (FoG) is related to emotional state and cognitive function. It was suggested then that a dysfunction in mobility - an unequivocally motor symptom - is in fact a cognitive, and therefore non-motor, symptom too.

The second plenary, and the final discussion, of the Meeting was led by D Burns (UK). Dementia has now been identified as a common and core feature of PD, typified by insidious onset and slow progression. Patients suffer from cognitive dysfunction, neuropsychiatric burden, and fluctuating attention. Prof Burns reviewed the numerous tools available to assess NMS in PD, and concluded that the Mini Mental State Examination is not sensitive. Instead, the use of the Addenbrooke's Cognitive Examination (ACE-R), the Montreal Cognitive Assessment, the Cornell Scale for Depression, and the various Neuropsychiatric Inventories (including NP4, 10, and 12) were recommended as screening tools. Diagnostic criteria take classical clinical features into account, but require prospective validation to ascertain a gold-standard.

The variability in methods of diagnosing dementia in PD is equalled by the range of treatment approaches, all of which are sub-optimal. The results from the use of Memantine in Lewy Body Dementia are awaited, whilst a large scale trial of Donepezil - MUSTARDD - is beginning shortly. Although supported only by a weak evidence base, Quetiapine is currently the first choice atypical anti-psychotic therapy for the treatment of dementia in PD.

The day was rounded off by the awarding of poster prizes and a brief vote of thanks by Professor K R Chaudhuri. The interpretation of symptoms and the description of Parkinson's Disease is now in a state of flux. Queries remain about the clinical relevance of the pathophysiology, the definition of the disease as a motor and non-motor complex, and the potential neuroprotective effects of treatment, to name just three fragments of a growing puzzle. The pioneering research presented at the Meeting was a testament to the exponential pace of research into PD. Fresh answers are generating new questions, and progress can only be made in an environment of translational medicine.