Institution: University College London

Unit of Assessment: 4 - Psychology, Psychiatry and Neuroscience

Title of case study: Parkinson's Disease – recognition, quantification and treatment of non-motor features

1. Summary of the impact

We established a comprehensive international collaboration to develop, validate and apply new scales for the identification and quantification of non-motor symptoms and signs in Parkinson's disease (PD). This was intended to provide tools to assess response to treatment, help define the clinical prodrome of PD and provide a means to evaluate novel therapies designed to modify the course of disease. The scales have been produced, validated and published. They have been incorporated as end points in international clinical trials for PD and have been introduced by specialist societies and NHS commissioners as a standard of care for PD patients.

2. Underpinning research

UCL has developed a major research programme in Parkinson's disease. This encompasses the basic sciences, clinical research and clinical trial development and execution. Parkinson's disease is a neurodegenerative condition that affects multiple areas of the brain as it progresses and produces motor symptoms (bradykinesia, rigidity, tremor) and a range of non-motor features that include cognitive impairment, autonomic dysfunction, psychiatric disturbances etc. **[1]**. These non-motor features dominate the patient's quality-of-life in mid to advanced Parkinson's disease. In addition, it has been recognised that certain non-motor features may precede the onset of motor symptoms and therefore the diagnosis of Parkinson's disease. This emphasised the potential importance of non-motor features in the pre-motor clinical prodrome of Parkinson's disease **[2]**.

The Department of Clinical Neurosciences has played a major role in research into the cause and treatment of Parkinson's disease and was the first to describe the mitochondrial contribution to this and other neurodegenerative diseases. From 1993, the Department led research on defining the role of mitochondria in neurodegeneration, specifically in Parkinson's disease, Huntington's disease and in Friedreich ataxia, publishing several seminal articles which are now citation classics (citations >400). As part of this research the pattern of neurodegeneration in these diseases and the corresponding clinical deficits became more clearly defined, and the Department played a leading role in this particularly in Friedreich ataxia. Novel scales for the assessment of ataxia and the impact on patient quality of life were developed. As part of this exercise, it became clear that there was also an unmet need in this area, specifically in the context of Parkinson's disease and its non-motor symptoms.

In 2006, the Department organised and co-chaired with Dr K Ray Chaudhuri (King's College London) the creation and development of the International Non-Motor Study Group for Parkinson's disease. The intention of this group was to develop patient-reported symptom scales and physician-recorded non-motor sign scales for the assessment and quantitation of non-motor features for use in clinical management, research and clinical trials.

The study group produced the non-motor symptom questionnaire (NMSQuest) and the non-motor symptom scale (NMSS) **[3]**. These were rigorously assessed for validity and reproducibility, and validated in several European and Asian languages. Both the questionnaire and symptom scale have been used in clinical trials as endpoints in the assessment of novel therapies for Parkinson's disease.

The questionnaire and scale have also been assessed in research to define the clinical prodrome of Parkinson's disease, particularly in certain stratified groups such as those with glucocerebrosidase mutations. This research has demonstrated that selective cognitive impairment and hyposmia precede the onset of motor dysfunction in this genetically determined group. The

non-motor questionnaire and symptom scale are now being used in conjunction with imaging to select those amongst this group who are particularly at risk of developing Parkinson's disease. These individuals will then be offered participation in a clinical trial of novel small molecule chaperones to enhance glucocerebrosidase activity and reduce alpha-synuclein levels **[4]**. Research from UCL suggests that such therapy may be generally applicable across the Parkinson's disease aetiology spectrum.

Thus the development of the non-motor symptoms scales has had significant implications for patient management, an understanding of the evolution of Parkinson's disease, clinical trials and in particular the development of disease modifying therapies.

3. References to the research

[1] Chaudhuri KR, Martinez-Martin P, Brown RG, Sethi K, Stocchi F, Odin P, Ondo W, Abe K, Macphee G, Macmahon D, Barone P, Rabey M, Forbes A, Breen K, Tluk S, Naidu Y, Olanow W, Williams AJ, Thomas S, Rye D, Tsuboi Y, Hand A, Schapira AH. The metric properties of a novel non-motor symptoms scale for Parkinson's disease: Results from an international pilot study. Mov Disord. 2007 Oct 15;22(13):1901-11. http://dx.doi.org/10.1002/mds.21596

[2] Martinez-Martin P, Schapira AH, Stocchi F, Sethi K, Odin P, MacPhee G, Brown RG, Naidu Y, Clayton L, Abe K, Tsuboi Y, MacMahon D, Barone P, Rabey M, Bonuccelli U, Forbes A, Breen K, Tluk S, Olanow CW, Thomas S, Rye D, Hand A, Williams AJ, Ondo W, Chaudhuri KR. Prevalence of nonmotor symptoms in Parkinson's disease in an international setting; study using nonmotor symptoms questionnaire in 545 patients. Mov Disord. 2007 Aug 15;22(11):1623-9. http://dx.doi.org/10.1002/mds.21586

[3] Chaudhuri KR, Rojo JM, Schapira AH, Brooks DJ, Stocchi F, Odin P, Antonini A, Brown RJ, Martinez-Martin P. A proposal for a comprehensive grading of Parkinson's disease severity combining motor and non-motor assessments: meeting an unmet need. PLoS One. 2013;8(2):e57221. http://dx.doi.org/10.1371/journal.pone.0057221. Epub 2013 Feb 27

[4] McNeill A, Duran R, Hughes DA, Mehta A, Schapira AH. A clinical and family history study of Parkinson's disease in heterozygous glucocerebrosidase mutation carriers. J Neurol Neurosurg Psychiatry. 2012 Aug;83(8):853-4. http://dx.doi.org/10.1136/jnnp-2012-302402

[5] Gallagher DA, Lees AJ, Schrag A. What are the most important nonmotor symptoms in patients with Parkinson's disease and are we missing them? Mov Disord. 2010 Nov 15;25(15):2493-500. http://dx.doi.org/10.1002/mds.23394

[6] Noyce AJ, Bestwick JP, Silveira-Moriyama L, Hawkes CH, Giovannoni G, Lees AJ, Schrag A. Meta-analysis of early nonmotor features and risk factors for Parkinson disease. Ann Neurol. 2012 Dec;72(6):893-901. http://dx.doi.org/10.1002/ana.23687

4. Details of the impact

Parkinson's disease is the second commonest neurodegenerative disease, now with a lifetime risk in the UK of 4%. Approximately 200,000 people suffer from PD in the UK (prevalence ~1/300). The treatment of PD is currently directed to improving the motor symptoms caused by dopamine deficiency. This is effective in the early stages of the disease, but with progression, non-motor, non-dopaminergic features such as cognitive, autonomic and psychiatric disturbances dominate and cause a significant deterioration of quality of life. Before our work in this area, there was little recognition of these non-motor features and no means to assess their prevalence, importance or measure their response to treatment. Physicians/neurologists in the clinic had no means to evaluate the extent and severity of this important aspect of PD, and patients had no way to communicate easily the type, severity and frequency of their non-motor problems. The scales that we have developed have provided clinicians with the tools to assess non-motor symptoms and our questionnaires have given the patient the method to convey the severity of the impact of their non-

motor features on their life. These aspects are crucial in delivering improved treatment and care to both the patient and more useful information to the care-giver.

Our scales have now been widely incorporated into clinical practice. For example, the National Parkinson's Audit Report 2011 noted that many services were using our questionnaire in preference to one of those recommended in the Occupational Therapy Best Practice Guidelines **[a]**. Use of the questionnaire is recommended by Parkinson's UK who have made it available in print and on their website. They recommend that: "*This is a questionnaire for people with Parkinson's to complete to help health professionals assess their non-motor Parkinson's symptoms. It should be completed before visiting your doctor or Parkinson's nurse"* **[b]**. The scale was incorporated into the Department of Health's 18-week commissioning pathway for Tremor (Parkinson's Disease) which recommended it as a quality of life outcome measure **[c]**. It is recommended in Scottish Guidelines on *Diagnosis and pharmacological management of Parkinson's disease* (SIGN 113) **[d]**.

Services treating PD require the questionnaire to be completed in advance, for example King's College Hospital: "What is required before referring a patient: For Parkinson's NMSQuest to be completed as per Department of Health 18-week pathway for Parkinson's (tremor)" **[e]**. Our clinical services for PD patients at both the Royal Free and UCLH now routinely use the non-motor questionnaire and scale as part of the holistic clinical evaluation of Parkinson's disease patients as a means to design therapeutic strategies at a personal patient level, and to evaluate the effect of the strategy. We are now working with the Chief Executive of Parkinson's UK and his team to develop the model for the UK's first 'UK Centre of Excellence' for the management pathway of Parkinson's disease to include non-motor assessment **[f]**. This model will then be rolled out across the UK.

The scales and questionnaires have been adopted by a number of societies and are widely recommended in guidelines. The International Parkinson and Movement Disorder Society (an international professional society of healthcare professionals) provides our questionnaire on their website **[g]**. The Parkinson Society of Canada has also produced two guides (one for patients and one for clinicians) which are based on the NMS questionnaire **[h]**. The Quality Standards Subcommittee of the American Academy of Neurology reported that: "*The NMS Quest study established a valid and reliable questionnaire to identify nonmotor symptoms in PD*" **[i]**. The scale is also recommended by the European Parkinson's Disease Association who say that: "*This 30-point questionnaire recognises that non-movement difficulties often occur in Parkinson's and that it is important for a doctor to be aware of their extent and the impact they have on life so that treatment takes these into account. Areas covered include sleep, Constipation, vision, smell, sexual problems and memory. The inclusion of such topics in the questionnaire has been found helpful in opening a dialogue on subjects that might otherwise be ignored or may be considered to be embarrassing*" **[j]**. The US Parkinson's Disease Non-Motor Group also provide the questionnaire **[k]**. The questionnaire has also been validated for use in other populations and translated accordingly. It is in use in Japan, North America and many countries in Europe.

The non-motor questionnaire and scale have recently been incorporated as secondary endpoints into international Phase II/III clinical trials for symptomatic treatment in Parkinson disease **[l]**.

5. Sources to corroborate the impact

[a] National Parkinson's Audit Report 2011: http://www.parkinsons.org.uk/sites/default/files/parkinsonsaudit_2011report.pdf see p. 46

[b] Scale available for download from Parkinson's UK: http://www.parkinsons.org.uk/content/non-motor-symptoms-questionnaire

[c] See screenshot at end of this section.

[d] www.sign.ac.uk/pdf/sign113.pdf See p. 8 and Annex 3.

[e] http://www.kch.nhs.uk/service/a-z/movement-disorders See tab "Referring to this service"

[f] Can be corroborated by the Chief Executive of Parkinson's UK. Contact details provided.

[g] http://www.movementdisorders.org/UserFiles/file/NMSS%2030%20items%20revised.pdf

[h] http://www.parkinson.ca/site/c.kgLNIWODKpF/b.8019621/k.2C45/NonMotor_Symptoms_of_Parkinsons_Disease.htm

[i] http://www.neurology.org/content/74/11/924.full

[j] http://www.epda.eu.com/en/parkinsons/in-depth/parkinsonsdisease/rating-scales/pd-nms-questionnaire/

[k] http://www.pdnmg.com/non-motor-symptoms.html

[l] For example:

- CLEOPATRA: www.ncbi.nlm.nih.gov/pubmed/17509486 (completed)
- RECOVER: www.ncbi.nlm.nih.gov/pubmed/21322021 (completed)
- ROPINIROLE: www.ncbi.nlm.nih.gov/pubmed/21699627 (completed)
- PANDA study: http://clinicaltrials.gov/ct2/show/NCT01439100 (in progress)
- DOLORES study: http://clinicaltrials.gov/ct2/show/NCT01744496 (in progress)