Institution: University College London

Unit of Assessment: 4 - Psychology, Psychiatry and Neuroscience

Title of case study: Improving the diagnosis and management of Dementia with Lewy bodies by imaging dopamine transporter uptake in the basal ganglia

1. Summary of the impact

Research at UCL has greatly contributed to the understanding of the dopaminergic system in Dementia with Lewy bodies (DLB) with an initial publication in Lancet 1999 showing that patients with DLB have reduced uptake of dopamine transporter compared to patients with Alzheimer's disease and that this could be a useful biomarker for DLB. Since then the research conducted on imaging of dopamine transporter uptake has had national and international impact and significantly contributed to a change made in the Revised Clinical Criteria for the diagnosis of Dementia with Lewy bodies (McKeith et al 2005) which now includes "low dopamine transporter uptake in the basal ganglia demonstrated by SPECT imaging" as a "suggestive feature" for DLB.

2. Underpinning research

Dementia with Lewy bodies (DLB) is a form of dementia that accounts for up to 15 per cent of all cases of dementia in older people. It affects over 100,000 people in the UK, and is increasing as the population ages. DLB is difficult to diagnose, and is frequently mistaken for Alzheimer's disease (AD). This leads to worse outcomes for patients, as prognosis, the course of the disease and the clinical management of DLB differ in some important aspects from other dementias such as Alzheimer's disease. The research programme described below aimed to address the problem of frequent misdiagnosis by developing a new brain imaging technique that measures dopamine transporter uptake in the basal ganglia.

Early work carried out by Dr Zuzana Walker at UCL tested the idea that imaging dopaminergic deficit in DLB (using the dopaminergic presynaptic ligand FP-CIT and single photon emission computed tomography – SPECT) had the potential to distinguish DLB from Alzheimer's disease. This was published as an autopsy case study in the Lancet **[1]**. The concept was further tested in a single centre study with initial autopsy results **[2]**. Following on from this research, other single centre studies (for example, a study conducted by O'Brien in Newcastle in 2004) replicated these results.

Over the five years following, we undertook a longitudinal follow-up of the original imaging cohort. This led to the largest published clinico-imaging-pathological cohort of patients with dementia and FP-CIT SPECT in the world. We demonstrated that dopamine transporter imaging has excellent sensitivity and specificity for the diagnosis of DLB when compared to the gold standard (i.e. autopsy diagnosis) **[3], [4]**.

In 2007 the diagnostic utility of dopamine transporter imaging in dementia was further confirmed in a large European multinational imaging trial involving 20 centres in 10 countries. This study was led by McKeith (Newcastle) and sponsored by GE Healthcare (who had provided the ligand, which is marketed commercially as DaTSCAN). Walker was a collaborator in the study and substantially contributed to the design, execution and publication. The results showed that dopamine transporter imaging has excellent sensitivity and specificity as a test (biomarker) for DLB **[5]**. The utility of dopamine transporter imaging by FP-CIT (DaTSCAN) SPECT was further confirmed in a one-year follow-up study of the original cohort of patients entered into this trial. The follow-up study concentrated on patients with possible diagnosis of DLB (some but not sufficient features of DLB to fulfil criteria for probable DLB) **[6]**.

Despite the excellent results of the FP-CIT (DaTSCAN) SPECT in distinguishing DLB from AD, results from a further study led Walker to urge caution when interpreting reduction in dopamine transporter imaging as a diagnostic biomarker of DLB in the differential diagnosis of

Frontotemporal Dementia and DLB **[7]**.

The results from the largest study of possible DLB cases come from a recently completed European study designed by Walker and sponsored by GE Healthcare entitled "DaTSCAN Imaging in Subjects with an Uncertain Diagnosis of Dementia with Lewy Bodies". The first results were published in an abstract in March 2013 at the American Academy of Neurology Meeting **[8]**. The new data show that DaTSCAN imaging indicated abnormal uptake in 43% of subjects with possible DLB at baseline. Physicians' confidence and ability to make a correct diagnosis of probable DLB significantly improved following dopamine transporter imaging by FP-CIT (DaTSCAN) SPECT.

3. References to the research

[1] Walker Z, Costa DC, Ince P, McKeith IG, Katona CL. In-vivo demonstration of dopaminergic degeneration in dementia with Lewy bodies. Lancet. 1999 Aug 21;354(9179):646-7. http://dx.doi.org/10.1016/S0140-6736(99)01178-2

[2] Walker Z, Costa DC, Walker RW, Shaw K, Gacinovic S, Stevens T, Livingston G, Ince P, McKeith IG, Katona CL. Differentiation of dementia with Lewy bodies from Alzheimer's disease using a dopaminergic presynaptic ligand. J Neurol Neurosurg Psychiatry. 2002 Aug;73(2):134-40. http://dx.doi.org/10.1136/jnnp.73.2.134

[3] Walker Z, Jaros E, Walker RW, Lee L, Costa DC, Livingston G, Ince PG, Perry R, McKeith I, Katona CL. Dementia with Lewy bodies: a comparison of clinical diagnosis, FP-CIT single photon emission computed tomography imaging and autopsy. J Neurol Neurosurg Psychiatry. 2007 Nov;78(11):1176-81. http://dx.doi.org/10.1136/jnnp.2006.110122

[4] Walker RW, Walker Z. Dopamine transporter single photon emission computerized tomography in the diagnosis of dementia with Lewy bodies. Mov Disord. 2009;24 S2:S754-9. http://dx.doi.org/10.1002/mds.22591

[5] McKeith I, O'Brien J, Walker Z, Tatsch K, Booij J, Darcourt J, Padovani A, Giubbini R, Bonuccelli U, Volterrani D, Holmes C, Kemp P, Tabet N, Meyer I, Reininger C; DLB Study Group. Sensitivity and specificity of dopamine transporter imaging with 123I-FP-CIT SPECT in dementia with Lewy bodies: a phase III, multicentre study. Lancet Neurol. 2007 Apr;6(4):305-13. http://dx.doi.org/10.1016/S1474-4422(07)70057-1

[6] O'Brien JT, McKeith IG, Walker Z, Tatsch K, Booij J, Darcourt J, Marquardt M, Reininger C; DLB Study Group. Diagnostic accuracy of 123I-FP-CIT SPECT in possible dementia with Lewy bodies. Br J Psychiatry. 2009 Jan;194(1):34-9. http://dx.doi.org/10.1192/bjp.bp.108.052050

[7] Morgan S, Kemp P, Booij J, Costa DC, Padayachee S, Lee L, Barber C, Carter J, Walker Z. Differentiation of frontotemporal dementia from dementia with Lewy bodies using FP-CIT SPECT. J Neurol Neurosurg Psychiatry. 2012 Nov;83(11):1063-70. http://dx.doi.org/10.1136/jnnp-2012-302577

[8] Walker Z, Padovani A, Thomas A, Inglis F, Tabet N, Rainer M, Pizzolato G, Moreno-Carretero E. A multicentre, randomised, open-label, comparative phase 4 trial to assess changes in dementia diagnostic category and diagnostic confidence after DaTscan imaging in subjects with an uncertain diagnosis of dementia with Lewy bodies (possible DLB). Neurology. 2013 May 7;80:e204. Available on request.

4. Details of the impact

Impact on clinical practice

The research described above has led to dopamine transporter imaging by FP-CIT (DaTSCAN) SPECT becoming the standard method of diagnosis for DLB around the world. In 2005, revised clinical criteria were issued by the DLB Consortium, which concluded that "*Low striatal DAT activity*

also occurs in DLB but is normal in AD, making DAT scanning particularly useful in distinguishing between the two disorders" **[a]**. In July 2006, the European indication for DaTSCAN (previously authorised only for patients with clinically uncertain Parkinsonian syndrome) was expanded to include differentiation of probable DLB from Alzheimer's Disease. In 2006, the method was incorporated into NICE clinical guidelines for dementia. These recommended that:

> "Dopaminergic iodine-123-radiolabelled 2-carbomethoxy-3-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (FP-CIT) SPECT should be used to help establish the diagnosis in those with suspected dementia with Lewy bodies (DLB) if the diagnosis is in doubt" **[b]**.

That this technique has now become standard clinical practice is shown by its inclusion in information provided in leaflets and online by Alzheimer's Research UK, who say "*To help make a specific diagnosis of DLB, a type of scan called a DaT scan may be used to look for changes in the brain which are more common in this type of dementia*" **[c]**. A 2011 paper from Southampton University Hospitals Trust which retrospectively reviewed 80 patients who had undergone FP-CIT (DaTSCAN) SPECT over a one-year period, concluded that "*It would seem that DaTSCAN imaging has a marked influence on the working clinical diagnosis and subsequent management of patients with suspected DLB*" **[d]**.

Impact on patients

Early, accurate diagnosis of DLB, in particular its differentiation from Alzheimer's disease, is important for optimal management. It may provide a better understanding of the symptoms and may induce changes in the clinical management of patients, allowing initiation of effective pharmacotherapy, and avoiding the consequences of neuroleptic sensitivity. Patients and carers can be provided with information about the likely symptomatology and illness course, which may help families, relatives and caregivers to make correct decisions and future plans. Altogether this translates into better management of patients with reduced carer burden and better clinical outcome.

FDA approval

In 2009, GE Healthcare submitted an application to the US Food and Drug Administration (FDA) requesting to license DaTSCAN for patients presenting with symptoms or signs suggestive of dopaminergic neurodegeneration. This application widely referenced the research described above, and Walker provided expert advice to the panel. The FDA concluded that the best clinical data provided for the application came from the autopsy study and the application was approved in August 2009 **[e]**.

Impact on guidelines

Walker contributed to guidelines issued in 2009 by the European Association of Nuclear Medicine on DaT SPECT imaging which recommended (citing the research described above) that "*[123I]FP-CIT imaging is indicated for the differentiation of dementia with Lewy bodies from other dementias*" **[f]**. Guidelines issued in 2011 by EFNS (European Federation of Neurological Societies) and ENS (European Neurological Society) cite our work in support of using 123I-FP-CIT SPECT for distinguishing DLB from non-DLB dementia **[g]**.

Industry investment in research

The FP-CIT (DaTSCAN) ligand belongs to GE Healthcare. There has been an active collaboration between GE Healthcare and UCL, with Walker being involved in the design and execution of a recent European study and with GE Healthcare sponsoring explorative investigator-led studies (Morgan et al 2013) and a PhD project within the group.

5. Sources to corroborate the impact

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[b] Dementia: Supporting people with dementia and their carers in health and social care. NICE clinical guidelines, CG42 - Issued: November 2006 http://www.nice.org.uk/CG42. See full guideline, p.22

[c] Alzheimer's Research UK webpages on DLB: http://www.alzheimersresearchuk.org/dementia-types/10001/dementia-with-lewy-bodies/#acc1/

[d] Kemp PM, Clyde K, Holmes C. Impact of 123I-FP-CIT (DaTSCAN) SPECT on the diagnosis and management of patients with dementia with Lewy bodies: a retrospective study. Nucl Med Commun. 2011 Apr;32(4):298-302. http://dx.doi.org/10.1097/MNM.0b013e328343d4ec http://dx.doi.org/10.1097/MNM.0b013e328343d4ec

[e] Briefing paper to FDA, referencing research in detail: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM176192.pdf

[f] European Association of Nuclear Medicine guidelines: Darcourt J, Booij J, Tatsch K, Varrone A, Vander Borght T, Kapucu OL, Någren K, Nobili F, Walker Z, Van Laere K. EANM procedure guidelines for brain neurotransmission SPECT using (123)I-labelled dopamine transporter ligands, version 2. Eur J Nucl Med Mol Imaging. 2010 Feb;37(2):443-50 http://dx.doi.org/10.1007/s00259-009-1267-x. Cites refs 3 and 4 above.

[g] Sorbi S, Hort J, Erkinjuntti T, Fladby T, Gainotti G, Gurvit H, Nacmias B, Pasquier F, Popescu BO, Rektorova I, Religa D, Rusina R, Rossor M, Schmidt R, Stefanova E, Warren JD, Scheltens P; EFNS Scientist Panel on Dementia and Cognitive Neurology. EFNS-ENS Guidelines on the diagnosis and management of disorders associated with dementia. Eur J Neurol. 2012 Sep;19(9):1159-79. http://dx.doi.org/10.1111/j.1468-1331.2012.03784.x See ref 129.