Institution: Newcastle University

Unit of Assessment: UoA 4

Title of case study: New diagnostic criteria and development of the DaTSCAN imaging technique for identification of dementia with Lewy bodies as a distinct condition.

1. Summary of the impact

Dementia with Lewy bodies (DLB) is one of the most common subtypes of dementia. Although DLB shares characteristics with Alzheimer's disease, the condition requires specific treatment and care. New diagnostic criteria generated at Newcastle allow diagnosis of DLB as a distinct condition from Alzheimer's, and these criteria have been incorporated into five national and international guidelines. The work also resulted in an accurate and sensitive diagnostic technique, commercialised by GE Healthcare as the DaTSCAN imaging tool, which is approved by the US Food and Drug Administration and the European Medicines Agency. These new diagnostic criteria allow appropriate treatment and management of DLB for the first time.

2. Underpinning research

Key Newcastle researchers (Where individuals left or joined the university in the period 1993-2013, dates given in brackets)

- Professor Ian McKeith. Professor of Old Age Psychiatry (1994-2010), Strategic Research Advisor (2010-date)
- Professor John O'Brien, Clinical Senior Lecturer/Consultant (1995-2000), Professor of Old Age Psychiatry (2000-2012), Strategic Research Advisor (2012-date)
- Professor David Burn, Clinical Senior Lecturer/Consultant (1994-2003), Reader (2003-2011), Professor of Movement Disorder Neurology (2006-date)
- Professor Elaine Perry, Honorary Professor (1991-2009), Strategic Research Advisor (2009-2011), Emeritus Professor (2012-date)
- Professor Robert Perry, Clinical Reader/Consultant (1980-1999), Clinical Professor/Consultant (1999-2009), Emeritus Professor (2009-date)
- Professor Jim Edwardson, Professor of Neuroendocrinology (2005-2012), Emeritus Professor (2013-date).

The challenge of dementia

Dementia affects 36 million people worldwide – 5.4% of those aged over 65 years – and the ageing population means that this figure is set to rise to 115 million by the year 2050. In financial terms, dementia has an annual cost of $315 billion worldwide, and in social terms the disease leads to 350 disability-adjusted life years per 100,000 persons (EV a). Dementia with Lewy bodies (DLB) is the second most common subtype of dementia after Alzheimer's disease (AD). Up to 20% of individuals are diagnosed with DLB at autopsy, which is equivalent to around 120,000 patients in the UK (EV b). The clinical prevalence of DLB is generally lower, at around 5% in patients over 75 years old, which suggests substantial under-diagnosis. The estimated incidence is around 0.1% a year in the general population, and 3.2% per year for all new dementia cases. Diagnosis of DLB is challenging, especially in the early stages before the full symptoms are present, which can lead to misdiagnosis and inappropriate treatment.

The two contributions of Newcastle research

Prior to the 1990s, dementia with Lewy bodies (DLB) was unsuspected or thought to be rare, and therefore no specific diagnostic criteria, treatment or management options were available. Starting in the 1990s, the first early contribution of Newcastle research was to identify DLB as a major cause of dementia in older people. The second contribution was to develop diagnostic criteria by carefully reviewing the clinical records of cases with pathologically-confirmed DLB post-mortem and describing the salient symptoms. This research revealed limitations in clinical diagnostic accuracy (R1 & 2) and identified the need for an *in vivo* biomarker. Analysis of earlier studies on

donated post-mortem material (R3) showed that patients with DLB (and those with Parkinson's disease dementia) had lower dopamine levels than control or AD patients, indicating that dopamine levels could be a suitable biomarker. In the early 2000s, Newcastle researchers carried out a clinical diagnostic imaging study (R4) and found that the dopamine deficit could be detected using a technique originally developed by GE Healthcare for the diagnosis of AD. The first step of the technique involves injection of the neuroimaging radiopharmaceutical drug ^{123}I-ioflupane (DaTSCAN). Next, the patient undergoes single photon emission computed tomography (SPECT) scanning to assess the uptake of the drug in certain areas of the brain. This provides visual evidence of dopamine transporter deficits, which is a common finding in DLB patients.

Dopamine transporter imaging was the first diagnostic tool to be licensed for the diagnosis of DLB and DaTSCAN was the first, and currently the only, diagnostic agent to be fully validated for identifying this disorder (R5). Studies carried out by Newcastle showed that this type of imaging could distinguish DLB from Alzheimer's disease. Newcastle research recently showed that it is useful in early or possible DLB cases where there is significant diagnostic uncertainty (R6).

3. References to the research (Scopus citation data as at 31.7.13, Newcastle researchers in **bold**)

1. **McKeith IG, Fairbairn AF, Bothwell RA, Moore PB, Ferrier IN**, Thompson P and **Perry RH** (1994). An evaluation of the predictive validity and inter-rater reliability of clinical diagnostic criteria for senile dementia of Lewy body type. *Neurology* 44: 872–877. DOI: 10.1212/WNL.44.5.872. **144 citations.**

2. **McKeith IG**, **Ballard CG, Perry RH, Ince PG, O'Brien JT, Neill D, Lowery K, Jaros E, Barber R, Thompson P, Swann A, Fairbairn AF and Perry EK**. (2000). Prospective validation of Consensus criteria for the diagnosis of dementia with Lewy bodies. *Neurology* 54: 1050–1058. DOI: 10.1212/WNL.54.5.1050. **268 citations.**

3. **Piggott, MA, Marshall EF, Thomas N, Lloyd S, Court JA, Jaros E, Burn D, Johnson M, Perry RH, McKeith IG, Ballard C and Perry EK** (1999). Striatal dopaminergic markers in dementia with Lewy bodies, Alzheimer's and Parkinson's diseases: rostrocaudal distribution. *Brain* 122: 1449–1468. DOI: 10.1093/brain/122.8.1449. **164 citations.**

4. **O'Brien JT, Colloby S, Fenwick J**, Williams ED**, Firbank M, Burn D,** Aarsland D and **McKeith IG** (2004). Dopamine transporter loss visualized with FP-CIT SPECT in differential diagnosis of dementia with Lewy bodies. *Archives of Neurology* 61: 919–925. DOI: 0.1001/archneur.61.6.919. **144 citations.**

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 and Reininger C. (2007). Sensitivity and specificity of dopamine transporter imaging with (123)I-FP-CIT SPECT in dementia with Lewy bodies: a phase III, multicentre study. *Lancet Neurology* 6: 305–313. DOI: 10.1016/S1474-4422(07)70057-1. **158 citations.**

6. **O'Brien JT, McKeith IG**, Walker Z, Tatsch K, Booij J, Darcourt J, Marquardt M and Reininger C (2009). Diagnostic accuracy of 123I-FP-CIT SPECT in possible dementia with Lewy bodies. *British Journal of Psychiatry* 194: 34–39. DOI: 10.1192/bjp.bp.108.052050. **42 citations.**

Relevant funding awards

- 1990 Novartis Pharmaceuticals £239,972. Prospective, multicentre, randomised double blind placebo-controlled exploratory study.
- 1990 Mental Health Foundation North East £1,000. Which patients with Lewy body dementia are at risk of severe side effects from major tranquillisers?
- 1999-2004 Medical Research Council (MRC) Dementia with Lewy bodies: Diagnosis and

Treatment £1,130,524.

- 2001-2002 Pfizer Limited. A pilot study into the effects of donepezil on cognitive impairment and neuropsychiatric features in patients with dementia with Lewy bodies and Parkinson's disease. £50,000.
- 2004 MRC £955,675. Support for Newcastle Brain Tissue Bank.
- 2005-2006. Seven consultancy payments from GE Healthcare, awarded to Professors O'Brien and McKeith, totalling £55,448.25.

4. Details of the impact

Impact of the research: overview

The two major impacts of the research have been: i) to distinguish DLB as a subtype of dementia that is distinct from AD, both pathologically and clinically, thereby allowing the development of diagnostic criteria (EV c); and ii) to develop the use of the DaTSCAN imaging tool to enable diagnosis (EV d, e, f). The ability to diagnose DLB is vital to determine appropriate treatment and management, since incorrect treatment can have severe, even fatal, consequences. For example, DLB patients show a positive response to cholinesterase inhibitors, but show severe adverse responses to neuroleptic medications and L-dopa (EV b, g, d). DLB patients often require more intensive care than AD patients; some DLB patients have symptoms that are specific to the condition, such as hallucinations and sleep disorders, which require specialist treatment (EV g).

Commercialisation of the DaTSCAN imaging tool for use in diagnosis of DLB

The research conducted at Newcastle, which showed that dopamine transporter imaging could distinguish DLB from AD, led GE Healthcare to adapt DaTSCAN (approved in 2000 as a diagnostic tool for AD, EV f) for use in the diagnosis of DLB. It was the first, and remains the only, SPECT imaging tool available that can distinguish between AD and DLB. In 2009, DaTSCAN was approved for use in DLB diagnosis by the Food and Drug Administration (FDA, EV e, which cites R2), and in 2011 the European Medicines Agency (EMA) granted market authorisation for the specific use of DaTSCAN to distinguish between DLB and AD (EV f). The 2011 EMA scientific discussion (EV d) includes R4 as one of two proof-of-concept studies included to assess whether DaTSCAN is a clinically useful tool to distinguish DLB from AD, and states that R4 does not show the "methodological weakness" associated with the other study included. This document states "*DAT scanning* [is] *particularly useful in distinguishing between the two disorders, as explained by McKeith et al. Hence DaTSCAN can be of particular value in … dictating future patient management… To conclude, the study results show that DaTSCAN can differentiate DLB from AD*."

Incorporation into national and international guidelines

Diagnostic criteria for DLB and the use of the DaTSCAN are now included in five national and international guidelines:

- European Association of Nuclear Medicine Neuroimaging Committee guidelines from 2009 (EV h) state "[DaTSCAN] *imaging is indicated for the differentiation of dementia with Lewy bodies from other dementias,*" citing R4 and R5.
- In 2010, DaTSCAN was included in the European Federation of Neurological Societies (EFNS) guidelines (EV a). It is the only diagnostic agent for any type of dementia that is given the highest level of evidence strength (I) and strength of recommendation (A): "*Dopaminergic SPECT imaging (FP-CIT or DATScan^{TM}, GE Healthcare, Amersham, UK) is useful to differentiate AD from DLB with sensitivity and specificity around 85% (I*)" and "*Dopaminergic SPECT is useful to differentiate AD from DLB (level A)*."
- The British Association for Psychopharmacology included R5 in their 2011 guidelines (EV b), stating that *"Dopaminergic SPECT … can distinguish DLB from AD (McKeith et al. 2007)*". The paper was accredited with the highest of four levels of evidence quality (type I) and was given a grade A recommendation.
- EFNS guidelines from 2012 (EV g) classified R6 as level II evidence, and accredited it with the second highest of four levels of evidence quality. These guidelines state that "*SPECT pre-synaptic dopamine transporter imaging is useful to distinguish DLB from non-DLB*

dementias", directly citing R6.

- The 5th edition of the authoritative diagnostic system "Diagnostic and Statistical Manual of Mental Disorders" (EV i), published in May 2013, includes an entire section on DLB ("*the criteria are met for major or mild neurocognitive disorder*", pg 618), and the use of SPECT in its diagnosis ("*a diagnostically suggestive feature is low…dopamine transporter uptake on [SPECT] scan*", pg 620), compared to only a brief mention in the 2000 version, and no recognised diagnosis in 1994.

Impact of the research on patients

The National Clinical Director for Dementia, NHS England, states that "*Since its approval for use in DLB by the Food and Drug Administration (FDA) in 2009, and European Medicines Agency (EMA) in 2011, the DaTSCAN has been widely used for diagnosis of DLB, both in the UK and worldwide. The DaTSCAN is a safe and quick method of obtaining an accurate diagnosis*." (EV j).

In summary, Newcastle work into DLB has led to the understanding that this disease is a separate subtype of dementia, with a distinct progression pathway and requiring specific treatment, care and management. The use of the FDA- and EMEA-approved DaTSCAN imaging tool is now incorporated into five guidelines, aiding diagnosis and allowing appropriate treatment and management of DLB.

5. Sources to corroborate the impact

EV a. Hort J, O'Brien JT, Gainotti G, Pirttila T, Popescu BO, Rektorova I, Sorbi S and Scheltens P on behalf of the EFNS Scientist Panel on Dementia (2010). EFNS guidelines for the diagnosis and management of Alzheimer's disease. *European Journal of Neurology* 17: 1236–1248.

EV b. O'Brien J and Burns A (2011). Clinical practice with anti-dementia drugs: a revised (second) consensus statement from the British Association for Psychopharmacology. *Journal of Psychopharmacology* 25: 997–1019.

EV c. McKeith *et al*. (2005). Diagnosis and management of dementia with Lewy bodies. *Neurology* 65: 1863–1872.

EV d. European Medicines Agency Scientific Discussion of DaTSCAN, 2011: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion_-_Variation/human/000266/WC500035354.pdf

EV e. Minutes from the Food and Drug Administration Drugs Advisory Committee 2009: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM191398.pdf

EV f. European Medicines Agency summary of the European public assessment report 2011: http://www.emea.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000266/WC500035348.pdf

EV g. Sorbi S *et al.* (2012). EFNS-ENS guidelines on the diagnosis and management of disorders associated with dementia. *European Journal of Neurology* 19: 1159–1179.

EV h. Darcourt *et al.* (2009). EANM procedure guidelines for brain neurotransmission SPECT using 123I-labelled dopamine transporter ligands, version 2. *European Journal of Nuclear Medicine and Molecular Imaging* 37:443–450.

EV i. The American Psychiatric Association, development of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders, http://www.dsm5.org/Pages/Default.aspx

EV j. Letter from the National Clinical Director for Dementia, NHS England, available on request.