Improving the accuracy of dementia diagnosis with functional imaging

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Neurodegenerative dementia is an increasingly common disease and places a significant burden on patients, healthcare professionals and healthcare systems. Neuropathological findings at autopsy confirm that 55 per cent of dementia is due to Alzheimer’s disease (AD), 11.2 per cent is due to dementia with Lewy bodies (DLB) and 8.8 per cent is due to vascular dementia. Mixed pathologies are common in one third of patients.¹

Additionally, there is an overlap in the neuropathology and clinical features between DLB and Parkinson’s disease (PD) dementia. Both are characterised by a loss of dopaminergic neurons in the substantia nigra in the midbrain and the presence of alpha-synuclein-positive Lewy bodies in the neurons.² Clinical symptoms also overlap, which makes it difficult to differentiate between AD and DLB in clinical practice. The sensitivity for detection of DLB based on clinical guidelines is still low (32.1 per cent) and many cases are misdiagnosed.¹

**Diagnosis of DLB**

As the second most common form of degenerative dementia in older people, DLB has a progressive decline in memory and cognition in common with AD.¹ In common with PD are motor symptoms, such as hypokinesia, rigidity and gait impairment. Differentiation between DLB and PD dementia can be established by the onset of dementia. Dementia within one year of diagnosis indicates DLB, whereas dementia in PD dementia occurs later (at least one year after diagnosis).² However, diagnostic accuracy and early differentiation between AD and DLB is essential for the treatment and prognosis of the disease. Importantly, patients with DLB have a severe sensitivity to neuroleptic drugs, with a two- to three-fold short-term increased mortality risk compared with all patients with dementia.³

The clinical diagnosis of DLB is based on consensus criteria with dementia as the central feature, as well as characteristic core features and supportive features (see Table 1), allowing for the diagnosis of either probable or possible DLB.² However, several studies have revealed a high specificity but low sensitivity for diagnosis based solely on clinical criteria and, in the early stages of the disease, a clinical diagnosis is even more uncertain.³

**Imaging DLB**

DLB neurotransmitter abnormalities have been characterised in post-mortem studies by quantitative autoradiography.⁶ In particular, a substantial loss of presynaptic dopamine transporters (DaT) in the putamen could be demonstrated by a reduced binding of dopaminergic radioligands in DLB and PD.⁷ These findings reflect the underlying pathophysiology, characterised by a degeneration of neurons in the substantia nigra and consequently, degeneration of the nigrostriatal pathway and its terminals in the striatum (putamen, caudate nucleus and nucleus accumbens).

Using autoradiography, the reduction of DaT ligand binding allowed for differentiation of PD (75 per cent reduction), DLB (57 per cent reduction), PD dementia, and AD dementia.⁴
as a biomarker for DLB

Table 1. Consensus criteria and features for the diagnosis of DLB

| Central features | ● Progressive mental decline interfering seriously with daily activities (memory impairment might not be prominent in early stages) |
| Core features | ● Fluctuating states of consciousness  
| | ● Recurrent visual hallucinations  
| | ● Spontaneous parkinsonism  |
| Suggestive features | ● Rapid eye movement (REM) sleep behaviour disorder  
| | ● Severe sensitivity to neuroleptics  
| | ● Dopaminergic abnormalities in basal ganglia on single photon emission computed tomography (SPECT) or positron emission tomography (PET)  |
| Supportive features | ● Repeated falls, syncope or unexplained loss of consciousness  
| | ● Severe autonomic dysfunction  
| | ● Systematised delusions  
| | ● Depression  
| | ● Hallucinations in other modalities  
| | ● Occipital hypoperfusion/hypometabolism  
| | ● Preservation of medial temporal lobe structures on CT/MRI  
| | ● Abnormal [123I] meta-iodobenzylguanidine (MIBG) myocardial scintigraphy  |
| Diagnosis | ● Probable DLB: Two core symptoms or one core symptom plus one suggestive symptom  
| | ● Possible DLB: One core or one suggestive symptom |

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Reduction), AD (no reduction) and controls (no reduction).7 Several tracers were investigated to demonstrate dopaminergic dysfunction of the nigrostriatal pathway in vivo with single photon emission computed tomography (SPECT) or positron emission tomography (PET). Presynaptic DaT was shown to be most promising, there is less conclusive evidence for the technique of targeting postsynaptic dopamine receptors.9

Ioflupane (123I) SPECT as a biomarker for DLB

In a seminal study, Walker et al (1999) demonstrated reduced DaT function in a patient with DLB compared with AD patients and healthy controls using ioflupane (123I) SPECT (DaTSCAN).8 Ioflupane (123I) is a cocaine analogue radioligand that binds to DaT in the plasma membrane of nigrostriatal neuron terminals.

A reduction in ioflupane (123I) uptake reflects nigrostriatal neurodegeneration associated with diseases such as PD, atypical parkinsonism and DLB, thus enabling differentiation from AD, essential tremor or drug-induced parkinsonism.9 Two studies have confirmed decreased ioflupane (123I) uptake in the striatum of patients with DLB and PD compared with patients with AD and healthy controls. DLB and AD patients could be clearly distinguished.10,11 AD patients showed a lower ioflupane (123I) binding than healthy controls in the contralateral posterior putamen (p<0.05).10 However DLB and PD could be separated only by their differential pattern of striatal dopaminergic dysfunction.11 Whereas patients with DLB had lower binding in the caudate nucleus compared with PD patients, FP-CIT uptake in the posterior putamen was decreased in PD compared with DLB.12

Visual ratings and semi-quantitative region of interest (ROI) analysis of the neuroimaging data revealed a good diagnostic discrimination between DLB and AD, but not between DLB, PD, and PD dementia.11 When correlated with autopsy-proven diagnosis, ioflupane (123I) imaging revealed a high sensitivity (83 per cent) and specificity (100 per cent) for detecting DLB in vivo.10

In a large multicentre study, sensitivity and specificity of ioflupane (123I) SPECT as a diagnostic biomarker for DLB were investigated further.13 Among 326 patients assessed, 94 matched the consensus criteria for probable DLB and 57 patients matched the criteria for possible DLB. Patients diagnosed with non-DLB dementia were mostly patients with AD. Mean sensitivity of ioflupane (123I) imaging for detecting probable DLB was 77.7 per cent (95 per cent CI 64.1-88.3). The mean specificity for excluding non-DLB dementia was 90.4 per cent (95 per cent CI 82.1-95.5). Furthermore, inter-reader agreement regarding visual assessment was high (Cohen’s k=0.87) and diagnostic accuracy was even greater than results from single centres.13

More recently, O’Brien et al (2009) have reassessed the same patients from the multicentre study in a 12-month follow-up study.14 They confirmed the high diagnostic accuracy of ioflupane (123I) SPECT as a biomarker for the detection of probable DLB. Reduction of striatal uptake remained stable in patients with probable DLB over one year. Furthermore, almost 43 per cent of cases with a clinical diagnosis of possible DLB and an abnormal scan at baseline were diagnosed as probable DLB in the follow-up measurement. This strongly suggests that a patient fulfilling the criteria of possible DLB and showing dopaminergic dysfunction in ioflupane (123I) SPECT might actually have probable DLB. Therefore the latest consensus criteria approved abnormal ioflupane (123I) SPECT as a suggestive feature enabling the diagnosis of probable DLB in patients with only one additional core feature.2
Ioflupane \(^{123}\text{I}\) SPECT images can be interpreted visually based on striatal activity (shape, intensity and symmetry). Figure 1 shows an example of ioflupane \(^{123}\text{I}\) SPECT imaging in a healthy person and a patient with DLB. Normal scans (A) reveal symmetric crescent-shaped striatal activity. In abnormal scans (B) activity is either asymmetric, absent or reduced in the putamen of either one or both hemispheres. In the example shown, there is no activity in the putamen of both hemispheres. Dopamine binding is reduced in the right caudate nucleus with respect to the left hemisphere which is visible as a circular or oval focus.

ROI-based analysis allows for a semi-quantitative analysis. Manually or automatically drawn ROIs are placed to encompass the caudate nuclei and the putamen, separately. Putamen/caudate nucleus ratios are calculated for each hemisphere. ROI-based analysis can show a slightly higher specificity compared with visual rating in a study differentiating between patients with AD and patients with DLB.\(^8\)

**Conclusion**

The improvement in sensitivity (77.7 per cent) with ioflupane \(^{123}\text{I}\) SPECT compared with the sensitivity of the clinical diagnosis (32.1 per cent) might lead to an early and accurate diagnosis of DLB enabling a correct prognosis and improved management of therapeutic interventions.\(^3\)\(^,\)\(^3\)\(^,\)\(^13\)

For example, alleviating cognitive decline and hallucinations with cholinesterase inhibitors or avoiding anti-psychotic drugs.\(^15\)

Having an accurate diagnosis is essential for patients and caregivers and helps improve understanding and the ability to deal with the significant symptoms of DLB.

**References**