

Early Discriminatory Diagnosis of Dementia with Lewy Bodies

The Emerging Role of CSF and Imaging Biomarkers

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Key Words

Dementia with Lewy bodies, early diagnosis ·
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Abstract

Background: The clinical diagnostic criteria for dementia with Lewy bodies (DLB) have a low sensitivity, and there are no generally accepted biomarkers to distinguish DLB from other dementias. Our aim was to identify biomarkers that may differentiate DLB from Alzheimer's disease (AD). **Method:** We performed a systematic literature search for studies of EEG, imaging techniques and genetic and CSF markers that provide sensitivity and specificity in the identification of DLB. **Results:** The best evidence was for scintigraphy of the striatal dopamine transporter system using FP-CIT SPECT. Several small scintigraphy studies of cardiovascular autonomic function using metaiodobenzylguanidine SPECT have reported promising results. Studies exploring innovative techniques based on CSF have reported interesting findings for the combination of amyloid β ($a\beta$) isoforms as well as α -synuclein, and there are interesting results emerging from preliminary studies applying proteomic techniques. Data from studies using structural MRI, perfusion SPECT, genetics and EEG studies show differences between DLB and AD but only at a group level. **Conclusion:** Several potential

biomarkers for the differential diagnosis of probable DLB and AD have shown good diagnostic accuracy in the research setting. Data from large multicentre studies and from studies with autopsy confirmation exist for scintigraphy of the dopamine transporter system. Future studies should explore its value in possible DLB and for clinical management and health economics.

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Definition and Epidemiology of Dementia with Lewy Bodies

Dementia with Lewy bodies (DLB) is defined clinically as dementia accompanied by the following core features: fluctuating cognition and consciousness, spontaneous features of parkinsonism and visual hallucinations. The main pathological features are Lewy bodies or Lewy neurites in brain stem nuclei, limbic structures and neocortex. Lewy bodies are intraneuronal cytoplasmic, eosinophilic and spherical inclusion bodies composed of α -synuclein and ubiquitin. They form the altered neurofilaments that accumulate after abnormal cleavage and phosphorylation of α -synuclein. Neurochemically, DLB is characterised by loss of cortical cholinergic markers and nigrostriatal dopamine loss [1].

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Although DLB was once considered rare, there is now widespread agreement that the condition is the second most common form of neurodegenerative dementia [Alzheimer's disease (AD) being the most common] and that it accounts for 10–20% of dementia cases seen in pathological dementia cohorts [1]. In 1 study, based on an unselected autopsy cohort, as many as 41% of individuals with dementia had a pathological diagnosis of DLB [2]. However, there is little robust epidemiological evidence on which to base estimates of DLB frequency, the available studies being limited mainly by inadequate definition of the source population and selection bias due to hospital-based sampling. The few population-based prevalence studies that have been reported generally lack a rigorous methodology for DLB diagnosis.

A recent systematic review reported that the prevalence of DLB was 0–5% in the general population and 0–30% in dementia cohorts; the DLB incidence (1 study only) was 0.1% per year in the general population and 3.2% per year among all new dementia cases [3]. Of note, dementia associated with Parkinson's disease (PD), a condition with similar clinical phenotype and brain changes as DLB [4], accounts for 3–4% of the total dementia population [5]. The relationship between dementia associated with PD and DLB is not yet established, and the current clinical distinction is based on the relative timing of parkinsonism and dementia; patients with dementia that develops before or within a year of the onset of parkinsonism are diagnosed as having DLB, whereas those who develop dementia a year or more after the onset of parkinsonism are diagnosed as having dementia associated with PD [4].

Why Is DLB Difficult to Diagnose?

Most studies based on the 1996 consensus criteria for clinical diagnosis of DLB [6] have reported a high specificity (80–100%) but a low sensitivity (20–60%) [1]; i.e. if a diagnosis of DLB was made, it was usually correct, but many cases were missed. The revised clinical consensus criteria, published in 2005, give greater diagnostic weight to clinical features suggestive of DLB, such as severe neuroleptic sensitivity and REM sleep disorder [7], but their sensitivity and specificity have not yet been explored.

DLB can be difficult to diagnose in the community because patients with early-stage disease usually present with attention, motor or psychiatric changes rather than reduced memory function, and the diagnosis is often missed on memory-based screening. Differential diagno-

sis of DLB is even more difficult in the later stages of the disease, when its presentation resembles that of other late-stage dementia types.

Furthermore, there is a lack of valid and reliable methods for assessing the core clinical features by which DLB is usually identified. Fluctuating consciousness can be particularly hard to diagnose reliably, with wide variations in the reported frequency and in the findings of different assessors looking at the same patients [8]. The assessment scales now available for neurodegenerative diseases offer improved psychometric properties [9] and include reliable tools for the assessment of parkinsonism, such as the Unified Parkinson's Disease Rating Scale [10], but several have a low inter-assessor reliability when applied to patients with dementia [11]. A modified version of the Unified Parkinson's Disease Rating Scale motor subscale has been developed for patients with DLB [12] but is not yet in widespread use. There is clearly a need for improved methods for assessing the key clinical features of DLB, to improve the accuracy of clinical diagnosis.

Finally, the brain pathology in patients with DLB is heterogeneous, leading to variations in the clinical phenotype. For example, the classical clinical features of DLB may be less prominent in patients with DLB, who have a greater burden of neocortical Alzheimer pathology, compared to those with pure Lewy body pathology [13]. Likewise, the presence of neurofibrillary tangles leads to a clinical presentation more typical of AD than DLB – i.e. a more classical amnesic syndrome in clear consciousness and less pronounced visual hallucinations or parkinsonism [13].

Why Is Early Discrimination of DLB Important?

A correct early diagnosis of dementia helps the physician to assess the individual's prognosis and make informed decisions on the best course of management [14]. It can be reassuring for patients and caregivers to know that the diverse range of symptoms, affecting modalities such as cognitive function, psychiatric health, motor function, sleep, attention and autonomy, are all part of a dementia syndrome due to a brain disease. A diagnosis of DLB also prompts the physician to check for additional DLB-specific symptoms that are not generally considered in other forms of dementia – e.g. visual hallucinations, which may not be voluntarily reported by the patient.

There is emerging evidence that DLB differs from AD in the disease course and treatment response experienced

by patients; thus early differentiation between the 2 forms of dementia is important for effective and safe management. Most importantly, people with DLB are at high risk of severe reactions to antipsychotic drugs [15]. Care should be taken when prescribing antipsychotics for any patient with dementia because of the possibility of an adverse event, but the risk of developing severe neuroleptic sensitivity reactions to typical and atypical antipsychotics, with motor and cognitive impairment, is much higher in DLB than in AD [16]. In addition, some patients with DLB may respond to dopaminergic treatment for parkinsonism [17], which has not been reported for AD, and which may be withheld in the absence of an accurate diagnosis.

Given the many different clinical symptoms of DLB, it is not surprising that patients with this type of dementia have more functional impairment [18] and a greater impairment of quality of life [19] than people with AD, even when the level of dementia is similar. Few adequately designed studies have compared the longitudinal disease course in DLB with that of other dementias. A recent clinico-pathological longitudinal study has reported a more malignant disease course, with a higher mortality rate and a trend towards shorter time to nursing home admission, in DLB compared to AD [20]. Similarly, the findings of a health-economics study have shown that the annual care costs are more than 100% higher for patients with DLB than for those with AD, despite a similar level of cognitive impairment in the 2 groups, the difference being driven mainly by a higher rate of institutionalisation for DLB [21]. Thus, compared to people with AD, patients with DLB suffer more, are more costly to society and need more frequent and careful follow-up.

Finally, as the underlying pathophysiological mechanisms leading to α -synuclein aggregation and Lewy body degeneration are unravelled [22], there is growing interest in developing disease-modifying drugs aimed at these pathological processes. Clinical and biomarker measurements can, in addition to their role in assessing disease progression, aid in the development and assessment of novel drug therapies.

Potential Biomarkers for DLB

The advantages of early diagnosis, combined with suboptimal clinical diagnostic accuracy, highlight the need for a valid biological marker for DLB. The objective of this study therefore was to review the literature to identify potential biomarkers that may distinguish DLB from

AD. We searched the MEDLINE database, using the phrase 'dementia with Lewy bodies' combined with: biomarkers (30 papers), EEG (17), imaging (109), MRI (47), SPECT (49), metaiodobenzylguanidine (MIBG) (16), genetics (134) and cerebrospinal fluid (CSF) (28). In addition, we searched reference lists from the papers identified and from relevant book chapters and proceedings from recent meetings. We read the abstracts of studies reporting on potential biomarkers in DLB and full papers reporting original studies of potential biomarkers. Sensitivity and specificity data, where provided, were recorded.

Role of EEG

EEG findings may be helpful in the diagnosis of people with dementia; for example, slowing of the EEG rhythm is a frequent finding in AD and other dementias. Spectral analysis of the EEG may be performed after transformation of the EEG from the time domain to the frequency domain, using the Fourier method, allowing determination of the exact amplitude or power values of different frequency bands. EEG coherence describes the similarity of electric function between 2 or more cortical sites.

Research on the differential diagnostic properties of EEG in dementia is sparse, and none of the published studies reports information about diagnostic sensitivity or specificity. At best, statistical differences between DLB and other patient groups or healthy controls are reported.

Several studies, based on small numbers of patients (some with inadequately described statistics), have shown more slowing of EEG rhythm in DLB than in AD. One study reported slowing of posterior EEG background rhythm and frontal dominant slow-wave burst patterns [23]. Another found frontal intermittent rhythmic δ -activity in 70% of patients with DLB and 22% of patients with AD and slowing of background EEG rhythm in 100% of patients with DLB and 66% of those with AD [24]. In another study, patients with DLB confirmed by autopsy showed a greater tendency towards slowing of both dominant and non-dominant EEG rhythm compared to patients with AD, and they more often had temporal slow-wave transients, which correlated with episodes of loss of consciousness [25]. In contrast, 2 studies reported no significant EEG differences between DLB and AD [26, 27], including the largest study, which involved 34 and 28 patients with DLB and AD, respectively.

There have been several EEG spectrum studies in DLB using Fourier analysis (quantitative EEG). Kai et al. [28],

in a study of power spectra and coherence, found that patients with DLB, but not those with AD, had an increased power density of the EEG in the δ - and θ -bands and a higher intrahemispheric coherence in fronto-temporo-central regions in the same bands. One study of the quantitative EEG correlates of fluctuating cognition showed a significantly higher variability in the slow δ -wave domain in patients with DLB than in those with AD or in healthy controls [29]. In another study, the variability in mean EEG frequency over 90-second intervals was larger in DLB than in AD or in healthy controls [30].

In summary, although EEG differences between DLB and AD have been reported, there is no evidence indicating sensitivity and specificity values, and thus EEG cannot serve as a biomarker for differentiating DLB and AD.

Genetic Testing

Exciting recent discoveries of causative and susceptibility genes for AD, fronto-temporal dementia and PD have raised the possibility of genetic testing for the differential diagnosis of dementia. Several mutations have been identified that lead to rare cases of familial PD [31] and AD [32]. The overlap of brain pathology between DLB and both AD and PD indicates a shared underlying pathophysiology, but the genetic basis of DLB has rarely been studied. However, the familial aggregation of DLB provides some evidence of genetic involvement in the development of the disease [33, 34].

Many patients with a clinical picture consistent with DLB have shown either mutations in the synuclein gene or positive correlations with the *APOE* ϵ 3/4 and ϵ 4/4 allele. Interestingly, mutations in the α -synuclein gene can lead to Lewy body formation and a phenotype of DLB as well as PD [33]. The argument for α -synuclein having a substantial role in DLB is further strengthened by its deposition in Lewy bodies and the fact that the Lewy body score is a diagnostic criterion for the disease [35] and is associated with cognitive decline in PD [36].

Patients carrying *LRRK2* mutations show a remarkably varying pathological pattern, ranging from pure degeneration without Lewy bodies to degeneration with widespread Lewy bodies and neurofibrillary τ -positive tangles [37, 38]. However, the clinical findings in affected individuals are typical for sporadic PD without major development of dementia [39]. The mechanisms by which mutations in the *LRRK2* gene cause PD and the reason why neuropathologic patterns fitting those of DLB are not accompanied by dementia still have to be determined, particularly since *LRRK2* could be a component of Lewy bodies in PD and DLB [40].

APOE ϵ 4 alleles are more common in AD than in controls and are associated with an earlier age of disease onset [41]. Findings regarding *APOE* polymorphisms in DLB have so far been inconclusive. Some studies show evidence for more frequent occurrence of ϵ 4 alleles in DLB compared to normal controls but similar to AD, indicating that DLB shares the *APOE* ϵ 4 allele with AD as a common risk factor, although there may be some differences in the way the ϵ 4 allele affects the phenotypic expression of disease [42, 43]. Others studies, however, have been unable to reproduce this finding and have shown a similar proportion of *APOE* ϵ 4 in DLB and controls [44], including a recent study with pathologic confirmation of the diagnosis [20].

Based on these findings, genetic testing is currently not a convenient source of candidate biomarkers for DLB.

CSF and Blood-Based Biomarkers

Although CSF may be a less appealing source of biomarkers because of the difficulty of obtaining samples, its physiological relationship with the brain makes it particularly interesting. It is well established that reduced concentrations of $a\beta$ peptide, combined with increased total and phosphorylated tau, has a good sensitivity and specificity in differentiating patients with AD from old people without cognitive impairment and from those with other dementias [45]. However, the potential of CSF biomarkers as a tool to distinguish between DLB and AD has been less well explored. Concentrations of $a\beta$ 1–42 have been reported to be higher in patients with DLB than in aged-matched controls [46], but the majority of sensitivity and specificity studies do not indicate that the levels of CSF $a\beta$ 1–40 or $a\beta$ 1–42 can usefully discriminate between DLB and AD [47]. There are only very limited data on longitudinal change or correlation with key clinical symptoms. One study identified an increase in $a\beta$ with disease duration but did not find an association with Mini Mental State Examination (MMSE) scores [46]. A better understanding of the relationship between $a\beta$ 1–40 or $a\beta$ 1–42 and clinical symptoms and disease course is essential if these biomarkers are to be of use in differential diagnosis.

Recent studies using innovative techniques to measure other $a\beta$ peptides have produced more promising results. In particular, a novel peptide suggested to represent an oxidised α -helical form of $a\beta$ 1–40 ($a\beta$ -ox) that may form as a result of the interaction between $a\beta$ peptides and α -synuclein was found to be significantly increased in DLB in a pilot study [48]. The findings were

similar in a subsequent validation study in a larger sample [49], in which the level of a β -ox was found to differentiate DLB from controls without dementia with a sensitivity of 88% and a specificity of 83%. Discrimination between DLB and other dementias was less accurate (sensitivity = 88%, specificity = 70%). Differentiation between DLB and AD was not reported. These findings are based on optimal ratios from post-hoc analyses and probably overestimate the discriminatory value of the a β peptide in question.

Other potentially interesting a β isoforms include a β 1–37 and a β 1–38 [48, 49].

Differences in total tau [50] and phosphorylated tau [47, 50, 51] appear to be more robust in distinguishing DLB and AD on a group basis, but the sensitivity of discrimination is still in the 70–80% range, and the large variability renders tau and phosphorylated tau less useful as potential diagnostic markers for individual patients [52].

Although α -synuclein, the key protein in the pathogenesis of DLB and PD, is predominantly intracellular, extracellular forms have been identified, including in CSF and plasma [53]. Reduced levels of α -synuclein in the CSF have been associated with increasing severity of parkinsonism in patients with PD [54], and preliminary findings have shown a significant increase in α -synuclein oligomers in plasma in patients with PD compared with controls [53]. In addition, initial studies indicate that people with DLB have lower CSF levels of α -synuclein than controls or people with AD [55, 56], but since these papers have not yet been reported in full, the sensitivity and specificity of CSF α -synuclein in the diagnostic discrimination of DLB and AD remain unclear. There are no direct assessments of α -synuclein in plasma from DLB patients.

The emerging body of work on α -synuclein is exciting, but further studies are needed to confirm the specificity of the antibodies, investigate alterations in specific isoforms, establish the pattern of changes in α -synuclein dimers and oligomers and elucidate the relationship with key clinical features.

Other candidate markers include indices of oxidative stress [57] and antioxidants [58], but the studies are contradictory and therefore difficult to interpret. A smaller body of work has suggested the potential utility of homocysteine [59] or mitochondrial markers [60], but the data are very preliminary. Autopsy and microarray studies have begun to highlight other potential biomarkers, such as heat shock proteins [61], but their potential value is not yet clear.

The development of genomics and proteomics allows identification of a large number of proteins and has the potential to accelerate the discovery of biomarkers for DLB and other neurodegenerative diseases. High sensitivity at 95% specificity has been reported in the first study to use proteomics to identify the simultaneous change of a large number of proteins in patients with DLB [62]. The authors identified more than 1,500 proteins in CSF from patients with AD, PD and DLB and controls. For each disease, more than 300 proteins were identified that differed from those in controls, of which about 100 were unique for each disease. Eight candidate proteins were selected for further testing as disease markers. Single markers with adequate sensitivity and specificity were found for AD and PD but not for DLB. However, the ability to distinguish between diseases increased when the markers were combined, 2 at a time, and became significant for DLB (sensitivity = 50% at 95% specificity) as well as for AD and PD. The potential value of this observation needs to be investigated further after the individual proteins have been identified and, given the small number of patients with DLB in the study, the findings need to be interpreted with caution. Thus, although currently not adequate for use, promising new techniques based on CSF protein analysis are emerging that may develop into useful biomarkers for the differentiation of DLB and AD.

DLB is a heterogeneous disease, involving several neurodegenerative processes, so it seems unlikely that 1 single biomarker will adequately distinguish it from other dementias. Further work is needed to understand how alterations in biomarkers relate to pathological changes in the brain and to clinical symptoms and to develop models based upon combinations of biomarkers that best characterise the profile of DLB.

Imaging Techniques

Structural MRI

Neuroimaging investigations, both structural (CT and MRI) and functional (SPECT and PET), may be helpful in the diagnosis of dementia, and emerging evidence suggests that some imaging techniques may be helpful in the differential diagnosis of DLB.

Dementia studies using structural MRI demonstrate patterns of cortical and subcortical atrophy and white-matter lesions. A characteristic pattern of atrophy has been identified in AD, with marked atrophy of the hippocampus and medial temporal lobe [63]. Among the few MRI studies involving patients with DLB, significant differences have been reported between DLB and AD; the

typical finding is preservation of the hippocampus and medial temporal lobe volume in DLB in comparison with AD [64–66]. These differences are based on group studies and cannot reliably distinguish DLB from AD on an individual level, demonstrated by the low reported sensitivity (40%) [65]. Other MRI changes, such as atrophy of the putamen [67] and the basal forebrain [68, 69], whole-brain atrophy [66], white-matter lesions and rates of progression of whole-brain atrophy [70], are even less specific and not helpful in the diagnosis.

A recent study – the largest to date in terms of patient numbers – used an automated voxel-based technique without specifying an a priori area of interest and found a signal pattern in DLB, involving focal atrophy of several areas, including the substantia innominata, hypothalamus and dorsal midbrain, indicating that this pattern of atrophy combined with a relatively preserved medial temporal lobe was suggestive of DLB [71]. Again, these were group data and there was substantial overlap between individuals in the AD and DLB groups. Sensitivity and specificity values were not reported. Thus, although it is useful in the diagnostic work-up of patients with dementia, structural MRI cannot yet be considered a good biomarker of DLB versus AD.

Perfusion SPECT

SPECT studies, with markers such as ^{99m}Tc -HMPAO, can be used to assess regional cerebral blood flow as a measure of cortical function. A characteristic pattern of occipital and parietal hypoperfusion – the so-called horseshoe sign – has been demonstrated in DLB [72]. This image differs from the pattern of reduced flow in parieto-temporal areas typically seen in AD.

Relatively few studies have explored the accuracy of SPECT in the identification of individual patients with DLB. In 1 early study, the diagnostic accuracy was relatively low, with sensitivity and specificity values of about 65% [72], while a more recent report has suggested higher rates of both sensitivity (81%) and specificity (85%) [73]. A diagnostic strategy combining SPECT and MMSE performance has produced a sensitivity of 81% and a specificity of 85% [74], although less encouraging results have also been reported [75].

Overall, the studies available suggest that occipital hypoperfusion on SPECT should raise suspicion of DLB, and some recent studies have reported good diagnostic precision. Large-scale multicentre studies are needed to establish if perfusion SPECT should be recommended as a biomarker for DLB. Similarly, fluorodeoxyglucose-PET studies have demonstrated reductions in occipital and

parietal glucose metabolism [76], but the technique is not yet available in many of the centres where dementia is diagnosed.

Cardiac Scintigraphy

Cardiovascular autonomic dysfunction is particularly common in DLB [77], and scintigraphy with ^{123}I -MIBG enables the quantification of post-ganglionic cardiac sympathetic innervation [78].

MIBG scintigraphy was introduced as a diagnostic tool for the involvement of the autonomous nervous system in diseases such as diabetic neuropathy and later in patients with PD (including early-stage disease [79]) and autonomic failure. Several studies using ^{123}I -MIBG scintigraphy have demonstrated reduced cardiac compared to mediastinal uptake in DLB, as opposed to AD [80–90]. In 2006, Yoshita et al. [84] reported that cardiac MIBG imaging could distinguish between clinically diagnosed DLB and AD with high levels of sensitivity and specificity, findings that have been replicated in 2 recent studies (table 1) [86, 89]. Moreover, MIBG has been found to be more accurate than occipital hypoperfusion using SPECT [87, 91] or CSF markers [89] as a means of discriminating between DLB and AD. Interestingly, pathological findings occur even in patients with DLB who have no parkinsonism [84].

If these findings can be confirmed in multicentre studies with large numbers of patients, MIBG scintigraphy may emerge as a useful tool in the early discrimination of DLB from AD. It should be noted, however, that a pathological MIBG scan can be difficult to interpret. Diseases such as diabetes, myocardial infarction, ischaemic heart disease and cardiomyopathy, which are common in the elderly, can damage the post-ganglionic sympathetic neurons, which may lead to false-positive MIBG findings.

Dopamine Transporter Imaging

One key neuropathological finding in DLB is the loss of dopamine transporter in the caudatum and putamen, which is a marker of loss of dopaminergic neurons in the substantia nigra [92]. Such loss can be detected by dopaminergic PET or SPECT, using ligands specific for the dopamine transporter, such as ^{123}I - β CIT and ^{123}I -FP-CIT, and assessed by visual rating, semi-quantitative and automated quantitative techniques. When used to distinguish PD from essential tremor, dopamine transporter imaging with both ligands has a sensitivity greater than 95% and a specificity above 80% [93]. Studies using ^{123}I -FP-CIT [94, 95] and ^{123}I - β CIT [96] have shown reduced

Table 1. Sensitivity and specificity of biomarkers for discrimination of DLB and AD

Biomarker and reference	Sensitivity %	Specificity %	Cases in study			Comments
			DLB	AD	NC	
<i>Cerebrospinal fluid</i>						
Phospho tau 181p [47]	74	85 ^a	60	94	60	
	80	79 ^b				
Ratio aβ 1–42 to aβ 1–37 [48]	71	74	21	21	23	more favourable sensitivity and specificity than previous publications from the same group; the degree of cohort overlap is unclear
Aβ-ox [49]	88	70 ^c	21	23	23	
Total tau and tau/amyloid quotient [46]	not reported	76 and 71	25	33	46	
<i>Structural MRI</i>						
Preservation of hippocampus and medial temporal lobe in DLB compared to AD [65]	38	100	26	28	26	
<i>SPECT</i>						
^{99m} Tc-HMPAO SPECT: occipital hypoperfusion and preserved medial temporal perfusion						
Lobotesis et al. [72]	65	87	23	50	20	
Shimizu et al. [73]	81	85	36	96		
Hanyu et al. [74]	85	85	20	75		combined with MMSE
Reduced activity of the striatal dopamine uptake site using ¹²³ I-FP CIT SPECT						
O'Brien et al. [94]	78	94	38	34		
McKeith et al. [99]	78	90	151	147		multicentre study
Walker et al. [97]	88	100	27	17	16	pathologically verified diagnosis
Decreased cardiac uptake on MIBG-SPECT: heart-to-mediastinum ratio of MIBG uptake						
Wada-Isoe et al. [89]	100	91	20	32	29	delayed ratio ^d
Yoshita et al. [84]	100	100	37	42	10	delayed ratio
Hanyu et al. [86]	95	87	32	40		

NC = Normal controls. ^a Discriminant analysis. ^b Classification tree. ^c DLB vs. all other dementias. ^d Uptake is assessed 20 min (early) and 3 h (delayed) after injection of ¹²³I-MIBG.

striatal dopamine transporter uptake in DLB, but not AD, suggesting that this method may be useful in the differential diagnosis of DLB.

Interestingly, an abnormal scan is seen also in patients who have DLB with no or mild parkinsonism [94], a condition that can be particularly difficult to distinguish clinically from AD. Parkinsonism does not occur until more than 80% of the dopamine nigral neurons have died, but dopamine transporter imaging can potentially identify involvement of the nigro-striatal system at an earlier stage. The usefulness of the test has also been shown in autopsy-proven cases [97], and a decline in binding with time has been demonstrated in longitudinal studies [98]. Of note, dopamine transporter scanning has been shown to have greater accuracy than clinical diagnosis [97].

These early promising findings have been replicated recently in a large multicentre trial using ¹²³I-FP-CIT as

a ligand [99]. Based on blinded visual reading of scans, the investigators report a sensitivity of 78% and a specificity of 90% for probable DLB versus non-DLB dementia (predominantly AD). These results led, in 2006, to approval by the European Agency for the Evaluation of Medicinal Products of FP-CIT SPECT in the differential diagnosis of probable DLB versus AD.

Imaging techniques based on dopamine transporter and other radiotracers can be affected by factors other than the primary biological process under study, so the correspondence between tracer uptake and diagnosis will never be 100% perfect. Future studies need to explore how dopamine transporter imaging performs in diagnostically uncertain settings and assess whether the test is useful in changing the clinical management of patients and whether it is cost effective.

Comments and Conclusions

DLB is a common form of dementia with a more malignant disease course and complicated management than AD. The clinical criteria for DLB have too low a sensitivity, and there is, therefore, a need for a biomarker to increase diagnostic accuracy. According to a consensus report, a biomarker should (1) be able to detect a fundamental feature of the disease; (2) be validated in neuropathologically confirmed cases; (3) be precise, with a specificity of 75–85% or greater; (4) be non-invasive; (5) be simple to perform, and (6) inexpensive [100]. A wide range of potential biomarkers for DLB exists, and promising results have been reported in studies of CSF protein analyses, structural MRI and perfusion SPECT. Several small, single-centre studies using scintigraphy with ^{123}I -MIBG, a measure of post-ganglionic sympathetic innervation, have demonstrated reduced cardiac compared to mediastinal uptake in DLB, as opposed to AD, with excellent sensitivity and specificity. To date, the most

compelling evidence has come from visualisation of striatal dopamine transporter activity, using ^{123}I -FP-CIT. This marker has demonstrated high sensitivity and specificity in a large multi-centre trial and in a small study with pathological confirmation of diagnosis, supporting the usefulness of this test in distinguishing DLB from AD. Future work, using modern techniques, will hopefully provide novel, accurate and less expensive biomarkers and explore whether a combination of different biomarkers can improve diagnostic accuracy.

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