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Dopamine Transporter Single Photon Emission Computerized Tomography in the Diagnosis of Dementia with Lewy Bodies

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Abstract: Dementia with Lewy bodies (DLB) is part of the spectrum of Lewy body disorders. However, it may be difficult to diagnose patients who have dementia but no Parkinsonism. Visual and semiquantitative assessment of the nigrostriatal dopaminergic nerve terminals in the putamen and caudate nuclei can be obtained with single photon emission computerized tomography (SPECT) using ligands that bind to the dopamine transporter molecule in the membranes of the nigrostriatal nerve terminals. This can be employed as a means of identifying subclinical degeneration of nigrostriatal neurones in patients with suspected DLB, increasing the probability of the diagnosis. In several studies, the sensitivity and specificity of abnormal dopamine transporter scans with regard to diagnosing probable DLB are better than 75 and 90%, respectively. This communication outlines the evidence for this and discusses some of the advantages, potential disadvantages, and areas of uncertainty with regard to the use of dopamine transporter SPECT in DLB diagnosis. © 2009 Movement Disorder Society

Key words: dementia; Lewy bodies; SPECT

PARKINSON'S DISEASE DEMENTIA AND DEMENTIA WITH LEWY BODIES

Movement disorder specialists will be all too familiar with seeing the emergence of hallucinosis, psychosis, confusional states, and dementia in patients with established Parkinson's disease (PD). Authorities in the past considered that dementia in PD (PDD) was not especially common, but well conducted population-based studies[1] have shown how common it is, to the extent that increasingly one suspects that anyone with PD who lives long enough will dement. The eye catching title of a recent paper refers to "the inevitability of dementia (in PD) at 20 years."[2] The situation is not diagnostically challenging, and no special investigation is necessary though a structural scan to rule out unexpected, unrelated conditions might be appropriate. The underlying neuropathology is diffuse Lewy body (LB) disease, with varying amounts of Alzheimer's pathology as well. Diagnostically much more challenging are patients with an identical type of neuropathology, who present with dementia, most likely not to movement disorder specialists but possibly to general neurologists, and certainly to dementia specialists including psychiatrists for the elderly. Some of these patients with dementia with Lewy bodies (DLB) will have readily detectable Parkinsonism, but others will have none, and the dementia itself may be difficult or impossible to distinguish clinically from other common dementias, particularly Alzheimer's disease, vascular dementia, and sometimes frontotemporal dementia. It is acknowledged that DLB and PDD represent different parts of a spectrum of LB disease, and that the dividing line declared by the consortium on DLB,[3] namely that patients developing dementia within one year of onset of Parkinson's disease have DLB, while those developing dementia later have PDD, is arbitrary.[4]

DIAGNOSING DLB

Although there are differences in the neuropsychological profile of cognitive deficits in dementia with Lewy bodies (DLB) when compared with other common

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dementias, they are not sufficient to allow the diagnosis to be made by assessment of the dementia alone. The "core features" of DLB are therefore of pivotal importance in making a clinical diagnosis. These are as follows: fluctuation of cognition; well formed and persistent visual hallucinations; and Parkinsonism which is "spontaneous," that is, not drug induced. If those features are clearly present, then the diagnosis can be made with confidence on clinical grounds, and the only investigations necessary are a structural brain scan and appropriate blood tests. However, fluctuation of cognition can be difficult to gauge, visual hallucinations are not entirely specific and Parkinsonism in DLB may be subtle or absent, at least in early disease, and in more advanced disease may be difficult to assess. Thus, there are many patients who present with dementia in whom DLB may be suspected, but in whom the distinction from Alzheimer's disease in particular cannot reliably be made. A specific imaging or biomarker test to identify significant LB pathology would be desirable. As yet, no such investigation exists. In an indirect manner, imaging that displays damage to the integrity of the nigrostriatal system goes some way toward being a means of detecting LB pathology.

FUNCTIONAL IMAGING OF THE NIGROSTRIATAL DOPAMINERGIC PATHWAY IN DLB

The use of functional neuroimaging of the nigrostriatal pathway in the diagnosis of DLB is predicated on the hypothesis that individuals with DLB who do not have definite Parkinsonism will nevertheless have loss of dopaminergic nigrostriatal neurones as a result of basal ganglion LB pathology. By contrast, in those with Alzheimer's disease, there will be no significant loss of nigrostriatal neurones. Robust evidence in support of this concept was in fact available from postmortem neurochemical studies at an early stage, when few imaging studies had been reported. Using ^{3}H-mazindol as a ligand to detect dopamine transporter in nigrostriatal nerve terminals in the caudate and putamen, a 57% loss was demonstrated in 25 DLB cases, whereas in 17 AD cases, there was no loss by comparison with controls.[5] Similar results were obtained in a different laboratory with ^{3}H-methoxytetrabenazine, a ligand that labels the vesicular monoamine transporter type 2.[6]

Either positron emission tomography (PET) or single photon emission computerized tomography (SPECT) can be employed to provide functional imaging of the nigrostriatal dopaminergic system in vivo. SPECT has the advantage of being more readily available and somewhat easier to organize and undertake, and the majority of the reported studies of imaging of the dopaminergic system in DLB have been SPECT studies, but PET has produced equivalent results.[7,8] With SPECT, the first ligand used was [^{123}I]-2β-carbomethoxy-3β-(4-iodophenyl) tropane (β-CIT). Subsequently, [^{123}I] N-ω-flouropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane (FP-CIT) became available. FP-CIT was preferable because the time interval between injection and scanning was just 3 hours, making the procedure possible on a single outpatient visit. Both ligands are cocaine analogues, which bind the dopamine reuptake and transporter molecule found in the presynaptic cell membrane of dopamine producing nigrostriatal nerve terminals in the striatum (caudate and putamen). Reduced binding reflects dysfunction or loss of nerve terminals, usually associated with loss of the neuronal cell bodies in the substantia nigra. The specific dopamine transporter binding of FP-CIT is somewhat lower than that of β-CIT which might make β-CIT advantageous in some borderline cases.[9] Clearly, the test is not specific with regard to the nature of the pathology in the substantia nigra, but Lewy body pathology is the commonest cause of major bilateral loss of substantia nigra neurones, with loss of ~50% of neurones being necessary before Parkinsonism becomes clinically detectable.[10] Table 1 summarizes the early and the larger more recent reported SPECT studies.

These studies show consistently and convincingly that in subjects with a clinical diagnosis of probable DLB, there is reduced binding of ligand in the putamen and caudate, and that in AD, the ligand binding is not significantly different from controls, suggesting strongly that FP-CIT SPECT would be effective in distinguishing DLB cases from AD cases when the distinction cannot be made confidently on clinical grounds. FP-CIT scans were abnormal in DLB cases without Parkinsonism, as well as in cases with Parkinsonism.[11,12] FP-CIT for SPECT has become commercially available, licensed in the European Union, marketed as ioflupane with the trade name DaTSCAN.

The weakness of all the studies in Table 1 (except reference 11) is that the diagnoses of DLB and AD were clinical, and therefore subject to error. An autopsy diagnosis has to be the gold standard, notwithstanding the uncertainties involved in the neuropathological diagnosis of both AD and DLB and the difficult issue of the coexistence of both disorders.[4] In applying the consensus clinical diagnostic criteria for probable DLB proposed by the consortium on DLB at their first international workshop,[3] the greatest accuracy when compared with subsequent autopsy diagnosis was

TABLE 1. *A summary of the main English language reported studies of dopamine transporter SPECT in DLB*[11–19]

Study	Ligand	Patients	Results	Comments
Donnemiller et al., 1997[14]	ß-CIT	6 DLB 6 AD 3 controls	Striatal binding reduced in AD but much lower in DLB with no overlap	Clinical diagnoses
Ransmayr et al., 2001[15]	ß-CIT	20 DLB 24 PD 10 controls	Striatal binding significantly lower in DLB and PD. Asymmetry more marked in PD than DLB	Clinical diagnoses
Walker et al., 2002[13]	FP-CIT	27 DLB 17 AD 19 early PD 16 controls	Striatal binding slightly reduced in AD; markedly reduced in DLB and PD	Clinical diagnoses
Ceravolo et al., 2003[16]	FP-CIT	20 DLB 24 AD	Striatal binding reduced in DLB compared with AD	Clinical diagnoses
Walker et al., 2004[17]	FP-CIT	21 DLB 19 early PD	Asymmetry of binding more marked in PD compared with DLB. Caudate binding reduction relatively greater in DLB compared with PD	Clinical (and some autopsy) diagnoses; same cohort as Walker et al., 2002
O'Brien et al., 2004[18]	FP-CIT	23 DLB 36 PDD 34 AD 38 PD 33 controls	Striatal binding reduced in DLB, PD, and PDD compared with AD and controls. Abnormal scan DLB versus AD: sensitivity 78%, specificity 94%. Relatively greater caudate loss in DLB and PDD compared with PD	Clinical diagnoses by consensus panel
Ceravolo et al., 2004[19]	FP-CIT	15 DLB 13 AD + Parkinsonism 20 PD 8 controls	Preserved striatal binding in AD + Parkinsonism	Clinical diagnoses
McKeith et al., 2007[12]	FP-CIT	88 DLB 144 non-DLB dementia (mainly AD)	Abnormal scan had 77.7% sensitivity and 90.4% specificity for DLB versus non-DLB dementia	Clinical diagnoses by consensus panel. Multicentre study
Walker et al., 2007[11]	FP-CIT	8 DLB 12 non-DLB dementia	Abnormal scan had 88% sensitivity and 100% specificity for DLB versus non-DLB dementia	Neuropathological diagnoses of all cases

achieved by the Newcastle upon Tyne group[20] (83% sensitivity, 95% specificity). In series from other centers, however, there was marked variation in specificity and particularly in sensitivity [see review Ref. [21]]. The estimated sensitivity and specificity of FP-CIT SPECT scan abnormality for a diagnosis of DLB versus AD will obviously be affected by the extent to which patients are wrongly categorized clinically.

AN AUTOPSY SERIES

Long-term follow up of a series of patients with dementia who had FP-CIT SPECT scans (mainly the same cohort as was reported previously[13]) and who subsequently had neuropathological examinations at autopsy has allowed a comparison of original clinical diagnosis, scan result, and autopsy diagnosis.[11] The published results were for 20 patients. We now have data for three further cases. Table 2 shows the data for these 23 cases. Scans were analyzed by a semiquantitative method using the ratio of FP-CIT binding in the striatum (caudate nucleus and putamen; the regions of interest) to nonspecific binding in the occipital cortex. An abnormal FP-CIT scan was defined as uptake below 2 standard deviations of the mean of controls in the worse affected posterior putamen. A number of observations can be made. Although it remains a small series, nevertheless, it is the largest published series of cases of patients with dementia for whom FP-CIT SPECT scan result and autopsy diagnosis are available. Evidently, the accuracy of clinical diagnoses was somewhat low (DLB being diagnosed overzealously). In mitigation, these were diagnoses applied at the time of first assessment of these patients, without the advantage of reappraisal over any length of time, and the diagnoses were made in clinic without recourse to a panel of experts. The concordance between the scan results and the neuropathological diagnoses is remarkable. With one exception, dementia and an abnormal FP-CIT scan was always DLB. The exception was a patient with a vascular lesion in the substantia nigra on one side, and in retrospect that should have led to correlation with a MRI scan at the time of SPECT scan analysis. Dementia with a normal FP-CIT scan was never DLB. In these 23 patients, the sensitivity of FP-CIT SPECT scan for diagnosing DLB was 100%, and the specificity was 92%. The mean time interval from scan to demise was 42 months, median 30 months, and range from 6 to 106 months. On the basis of these findings, one would expect that FP-CIT scan-

TABLE 2. *Comparison of initial clinical diagnosis, FP-CIT SPECT scan result, and ultimate neuropathological diagnosis*

	Initial clinical diagnosis	Autopsy examination	Baseline scan
1	AD	DLB + *AD*	Abnormal
2	DLB	DLB	Abnormal
3	DLB	DLB	Abnormal
4	DLB	DLB + *AD* + *CVD*	Abnormal
5	CBD	DLB + *AD*	Abnormal
6	DLB	DLB	Abnormal
7	DLB	DLB + *focal CVD*	Abnormal
8	DLB	DLB	Abnormal
9	DLB	DLB	Abnormal
10	DLB	DLB	Abnormal
11	AD	AD + *focal CVD*	Abnormal
12	AD	AD + *focal CVD*	Normal
13	DLB	AD + *haemorrhagic infarcts*	Normal
14	DLB	AD	Normal
15	DLB	CBD	Normal
16	DLB	AD	Normal
17	AD	Unspecified + *focal CVD*	Normal
18	AD	AD + *focal CVD*	Normal
19	DLB	FTD *lacking distinctive features*	Normal
20	DLB	AD	Normal
21	DLB	AD + *focal CVD*	Normal
22	AD	AD + *focal CVD*	Normal
23	AD	FTD-U	Normal

The clinical diagnosis made at first encounter (column 2) is compared with the dopamine transporter scan result obtained at that time (column 4) and the subsequent neuropathological diagnosis (column 3; DLB consortium criteria, 2005) in a series of cases with dementia that underwent scanning and ultimately autopsy. In columns 2 and 4, a light green background highlights cases in which the clinical diagnosis or scan result is concordant with the neuropathological diagnosis, while a pink background indicates cases where the clinical diagnosis was incorrect or the scan gave the "wrong" result. In column 3, the main neuropathological diagnosis is in bold type, and subsidiary diagnoses are in italics. CVD is cerebrovascular disease. In this analysis, scans were assessed semi-quantitatively (regions of interest method) and an abnormal FP-CIT scan was defined as uptake below two standard deviations of the mean of controls in the worse affected posterior putamen.

ning would be a powerful supportive investigation in diagnosing DLB.

In 2003, the third international workshop of the DLB consortium changed the diagnostic criteria for the clinical diagnosis of DLB. A new category called suggestive features was proposed. Neuroleptic sensitivity was elevated from supportive to suggestive and was joined by two newcomers, REM sleep behavior disorder and low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET.[4]

ACTUAL AND POSSIBLE ADVANTAGES AND DISADVANTAGES OF DOPAMINE TRANSPORTER SPECT IN DLB DIAGNOSIS

FP-CIT SPECT scanning has a number of favorable aspects. SPECT is widely available, in district general hospitals as well as large academic centers. We know from the European multicenter study[12] that consistent results can be obtained using a wide range of scanners. Although semiquantitative analysis of scans has the attraction of rigor, simple visual rating is as effective (ideal is both). On the other hand, given that patients presenting with dementia will have a structural scan (generally MRI), any need for a dopamine transporter scan necessitates a second scanning procedure. Cost and radiation exposure are considerations. Very recently, it has been claimed that the distinction between DLB and AD can be made on the basis of MRI alone, relying on differences in the extent of medial temporal lobe atrophy.[22] However, the reported patients had at least moderately advanced disease and a rather short interval between scan and death, and the AD group was significantly older than the DLB group.

The possibility of false positive and false negative scans obviously has to be a cause of concern. In our small autopsy series, there was only a single false positive, caused by cerebrovascular disease. Careful SPECT scan analysis and correlation of the result with a good quality structural scan ought to reduce the likelihood of this error. However, there are other possible sources of false positive scans. Frontotemporal dementia may be associated with Parkinsonism. A small series of 6 patients, who met clinical diagnostic criteria for both FTD and DLB, was reported recently.[23] Unfortunately, none of the patients had dopamine transporter scans. Perfusion scans in 5 of the patients were indicative of FTD. Two autopsies became available. Parkinsonism had been a clinical feature in both cases. Both had neuronal loss and gliosis in the substantia nigra, raising the possibility that dopamine transporter scans would have been abnormal. Neither case had LB pathology. Both had evidence of TDP-43 proteinopathy and a neuropathological diagnosis of frontotemporal lobar degeneration with ubiquitin immunoreactive changes (FTLD-U) type 1. On the other hand, our case of FTLD-U (case 23) had a negative FP-CIT scan. In 7 FTD cases, abnormality of FP-CIT scans was found, but no comparison with DLB was made.[24] Other dementias that may be associated with abnormal dopamine transporter scans include corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP). Abnormality of FP-CIT SPECT was reported in 8 of 8 CBD cases,[25] but is not invariable [case 15 in our series; (Ref. 26)]. Abnormal dopamine transporter scans are a feature of PSP[27] but ordinarily one would expect to be able to distinguish PSP from DLB on clinical grounds.

The coexistence of AD pathology and LB pathology poses difficulties for the diagnostic criteria of DLB,[4] and has implications for the significance of abnormal dopamine transporter scans. Not more than a third of DLB cases have "pure" LB pathology. Many have significant amounts of amyloid though often with relatively few neurofibrillary tangles. Some cases have copious Alzheimer's pathology. A patient with dementia with brainstem predominant LB pathology and advanced stage Alzheimer's pathology might perhaps have an abnormal dopamine transporter scan but on the basis of probability[4] neuropathologically AD might be judged to be the main cause of the dementia.

Conversely, there are situations where dopamine transporter scans might be falsely negative in DLB. One such might be very early disease. However, the prodrome of DLB remains undefined and so currently it is unlikely that patients with mild cognitive impairment or early behavioral or affective disorder will have dopamine transporter scans. Perhaps of greater concern is the possibility that LB pathology can start in the cortex and spare the brainstem and basal ganglia. Hitherto, such cases were reported sparsely, but they feature quite prominently (8% of brains with LB pathology) in a population-based study.[28]

By contrast with amyloid, imaging of alpha-synuclein is not expected soon, if ever, because it is intracellular. If it existed, would dopamine transporter imaging become redundant? Possibly not, because the mere presence of Lewy bodies does not mean that brain function is impaired. Lewy bodies need to cause neuronal damage or loss for disease manifestations to appear.[29]

WHICH PATIENTS WITH DEMENTIA SHOULD HAVE A DOPAMINE TRANSPORTER SPECT SCAN?

Ideally every patient with dementia deserves as accurate a diagnosis as possible. Accordingly, in any patient whose dementia diagnosis is uncertain and who could possibly have DLB a dopamine transporter SPECT scan is a consideration. Most such patients will fulfill clinical diagnostic criteria for "possible DLB" (dementia plus one core feature; or dementia plus one or more "suggestive" features,[4] but obviously excluding abnormal dopamine transporter scan which is currently one of the suggestive features). The effectiveness of FP-CIT in contributing to the diagnosis of DLB in this situation has recently been convincingly shown.[30] Most patients with clinically typical DLB do not need a FP-CIT scan. However, there are patients who fulfill diagnostic criteria for probable DLB, but where there are complicating factors such as cerebrovascular disease or medication with extrapyramidal adverse effects, and in such situations, a dopamine transporter scan can clarify the diagnosis. Finally, there are patients who have mild cognitive impairment (not dementia) and in addition have features raising the possibility of DLB (such as visual hallucinations, fluctuating cognition, and neuroleptic sensitivity). In these cases, recurrent delirium may be a concern, leading to repeated investigations. An abnormal FP-CIT scan can be diagnostically helpful and possibly cost effective.

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