

The Role of Radionuclide Studies in the Differential Diagnosis of Dementia with Lewy Body (DLB)

Brockhuis B¹, Slawek J², Wiczorek D³, Ussorowska D⁴, Derejko M⁵, Romanowicz G¹

¹Department of Nuclear Medicine, Medical University, Gdansk, Poland

²Department of Neurosurgery, Medical University, Gdansk, Poland

³Department of Rehabilitation, Medical University, Gdansk, Poland

⁴District Hospital for Nervous and Mental Diseases, Gdansk, Poland

⁵Department of Neuroelectrophysiology, Institute of Psychiatry and Neurology, Warsaw, Poland

Abstract

Dementia with Lewy Body (DLB) is considered to be the second most common (20%) neuropathological cause of degenerative dementia after Alzheimer's disease (AD). Typical clinical features of DLB include a progressive and fluctuating cognitive impairment and visual hallucinations along with Parkinsonian symptoms. Early diagnosis is important in DLB because of dangerous neuroleptic sensitivity which is associated with increased morbidity and mortality. Cholinergic deficit in DLB is more extensive when compared with AD. This might explain the beneficial effect of therapy with cholinesterase inhibitors, with improvement of cognitive and psychiatric functions. The functional neuroimaging with the use of SPECT and PET may contribute to the clinical diagnosis and understanding the possible pathogenesis of DLB. There are many similarities between DLB and AD with pronounced parietotemporal hypoperfusion whereas occipital hypoperfusion is more pronounced in DLB. Using tracers for presynaptic dopamine transporters such as I-123 β -CIT recent studies have found severely impaired dopaminergic function in DLB, similar to Parkinson Disease (PD) but not present in AD. Authors present a review of current literature on the role of SPECT and PET imaging in the diagnosis of DLB and three illustrated cases of probable DLB with rCBF SPECT scanning showing mostly parieto-occipital hypoperfusion.

Key words: Dementia with Lewy Bodies, radionuclide imaging

World J Nucl Med 2006;5:82-92

Correspondence:

Bogna Brockhuis

Department of Nuclear Medicine

Medical University,

ul. Debinki 7, 80-211 Gdansk, Poland

e-mail: bogna.brockhuis@interia.pl

Introduction

Dementia with Lewy Bodies (DLB) is the second most common type of degenerative dementia after Alzheimer's disease (AD) and accounts for 15-29% of all autopsy-confirmed dementias in old age (1). Mean age at the time of disease onset ranges between 60 and 68 years. The male gender prevails, disease duration is 6-8 years. The differential diagnosis of DLB is mostly with dementia of Alzheimer type, Parkinson disease (PD) and vascular dementia. Occasionally it may be necessary to distinguish DLB from progressive supranuclear palsy, multiple system atrophy and rarely Creutzfeldt-Jacob disease (2).

The characteristic clinical features of DLB include fluctuating cognitive impairment, visual hallucinations and extrapyramidal motor symptoms (Parkinsonism). One of these core features has to be present for a diagnosis of possible DLB, and two for probable DLB. Supportive features may increase diagnostic sensitivity and exclusion criteria need to be considered (3). Following Consensus in Newcastle in 1996: dementia with Lewy body is preferred term over "Lewy body variant of Alzheimer's disease" (4). Consensus criteria for clinical diagnosis of DLB are showed in Table 1. The specificity of Consensus criteria has been reported to range from 29% to 100% and the sensitivity from 22% to 90% (5). Early diagnosis of DLB is of special importance because of dangerous hypersensitivity for neuroleptics which results in increased morbidity and mortality. On the other hand, most of patients respond well to cholinesterase inhibitor therapy which improves both cognitive and neuropsychiatric symptoms (6,7).

Neuropathological diagnostic criteria

Lewy bodies were described for the first time by German pathologist Friedrich Lewy in 1913. He observed them in the brainstem of patients with paralysis agitans (Parkinson's disease). The same inclusions in substantia nigra were noticed by Tretiakoff and were called Lewy body (LB) (8). Pathologically, Lewy bodies (LB) are

1. The central feature required for diagnosis of DLB is a progressive cognitive decline of sufficient magnitude to interfere with normal social and occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention and of frontal-subcortical skills and visuospatial ability may be especially prominent.
2. Two of the following core features are essential for diagnosis of probable DLB and one is essential for possible DLB:
 - a. fluctuations of cognition with pronounced variations in attention and alertness
 - b. recurrent visual hallucinations that are typically well formed and detailed
 - c. spontaneous motor features of parkinsonism
3. Features supportive of the diagnosis are:
 - a. repeated falls
 - b. syncope
 - c. transient loss of consciousness
 - d. neuroleptic sensitivity
 - e. systematized delusions
 - f. hallucinations in other modalities
 - g. REM sleep behavior disorder
 - h. depression
4. A diagnosis of DLB is less likely in the presence of:
 - a. stroke disease, evident as focal neurological signs or on brain imaging
 - b. evidence on physical examination and investigation of any physical illness or other brain disorder sufficient to account for the clinical picture

Table 1. Consensus Criteria for Clinical Diagnosis of Probable and Possible DLB (3)

rounded eosinophilic intracellular inclusions, containing - synuklein as the main component. They are found within brain stem nuclei in PD (9). The first case report on DLB published in 1961 by Okazaki et al was on a patient with tetraparesis and dementia. Authors reported multiple Lewy bodies scattered diffusely in the patient's cerebral cortex. They were the first investigators who discussed a possible role of Lewy bodies in the pathogenesis of dementia (10). Contrary to PD, in DLB Lewy bodies are widely distributed throughout the cerebral cortex and are seen in substantia nigra and other subcortical regions. The cortical LB are usually found in small neurons of the deeper layers of temporal, frontal, and insular cortex affecting more or less all lobes. Cortical LB may also be found in PD, but to a lesser degree. For this reason it has been suggested that presence of more than five cortical LB in each visual field at a magnification of 100x is necessary for the diagnosis of DLB (11).

LB may also be found extracranially in the peripheral nervous system such as in the gastrointestinal tract, cardiac plexus, adrenal medulla, celiac ganglion, pelvic plexus and sympathetic ganglia (12,13,14,15). With respect to neuropathological findings two distinct forms of DLB have been defined: (1) the pure form presenting with LB only in cortical and subcortical structures and (2) the common form characterized by LB accompanied by senile plaques and neurofibrillary tangles (9,16,17).

Differential diagnosis

DLB shows clinical and pathological features overlapping with AD and PD (18,4,19), specially the variant of PD with dementia. Clinical and pathological differences between early stages of PD, DLB and AD are presented in Table 2 and 3 (2). In advanced stages the differentiation might be more difficult and DLB may be diagnosed retrospectively, if memory deficits and hallucinations preceded or appeared within the first year along with Parkinsonian symptoms.

The major neurochemical difference between AD and DLB is in the dopaminergic metabolism. Piggott et al. in their post-mortem studies in patients with DLB, PD, AD and elderly controls revealed significantly reduced binding to dopamine uptake sites (presynaptic receptors) in the caudal putamen in DLB compared with controls (57%), but not as extensive as in PD (75%), and unchanged in AD. The concentration and distribution of dopamine were disturbed in both DLB and PD. The loss of dopamine in DLB was diffusely uniform all over putamen, whereas in PD it was greater in the caudal part. In DLB patients there was 72% reduction in the dopamine concentration in the caudal putamen, whereas about 90% in PD (22). Those changes of dopaminergic metabolism are relevant to the interpretation of the in vivo imaging and diagnosis of DLB.

	PD	DLB	AD
Disease onset	64 years	60/68 years	67 years
Disease duration	13 years	6-8 years	7-9 years
Sex (m/f)	60/40	64/36	40/60
Tremor	85%	55%	<5%
Rigidity	100%	100%	85%
Akinesia	100%	100%	75%
Myoclonus	0%	18%	20-30%
L-Dopa effect	100%	75%	0%
Dementia	20-30%	100%	100%
Memory impairment	low	severe	< severe
Visuo-spatial disturbances	low	severe	>severe
Frontal syndrome	low	severe	>severe
Visual hallucinations	0*	16-83%	0-25%
Acoustic hallucinations	0*	11-45%	0-3%
Delusions	0*	50%	27%
Depression	27-70%	14-46%	0-17%

*at the disease onset

Table 2. Comparative clinical features of PD, DLB and AD (2)

	PD	DLB	AD
Senile plaques density	-	++	++
Tangles density	-	+	+++
Subcortical LB	+++	++	-
Cortical LB	+	+++	-
Cholinergic deficit*	+	+++	++
Dopaminergic deficit	+++	++	-

+++ typical manifestation of the disease, ++ usually present, + present, - unusual manifestation

* the cholinergic deficit in PD with dementia (PDD) is more severe than in AD and similar to DLB(21).

Table-3. Neuropathological and neurochemical differences among PD, DLB and AD (20)

Structural neuroimaging

The criteria for diagnosis of dementia with LB do not include neuroimaging methods (4). MRI studies on DLB are rare, mostly published by Barber et al. In volumetric study by Barber et al. (23) there were no differences in brain atrophy in patients with DLB compared with corresponding age matched control subjects. Similarly, in another volumetric MRI analysis of caudate nucleus there was no significant difference between patients of DLB, AD and vascular dementia (24). The purpose of the study in patients with DLB, AD and vascular dementia was to determine the diagnostic utility of medial temporal lobe atrophy (MTA) in the differential diagnosis of dementia. It has been confirmed that patients with DLB have significantly greater MTA than control group, but significantly less than that in patients with AD. This preservation of medial temporal structures may be useful in the differentiation of DLB from AD and vascular dementia. The absence of MTA may suggest DLB (25). In this study the analysis of white matter lesions in T2-weighted images in DLB, AD, vascular dementia and normal aging has revealed that white matter

and basal ganglia hyperintensities were more frequent and severe in patients with vascular dementia than in patients with AD and DLB. Periventricular hyperintensities were positively correlated with age and were more severe in all dementia groups than controls (26). MRI studies do not show any typical pattern in DLB and MTA may be only a supportive feature for the differential diagnosis between DLB and AD.

To our knowledge no study has been reported so far on using functional magnetic resonance procedures such as magnetic resonance spectroscopy or diffusion weighted magnetic resonance imaging in the differential diagnosis of DLB and AD.

Functional Neuroimaging:

rCBF SPECT study

DLB has not been examined so extensively with PET and SPECT as other atypical Parkinsonian disorders. Varma et al. in the first Tc-99m HMPAO study in the group of patients fulfilling clinical criteria for DLB have shown bilateral posterior cortical blood-flow hypoperfusion, a

Reference	No of all pts	SPECT results in DLB and N (No. of Patients studied)	SPECT results in AD and N (No. of Patients studied)	Remarks
Varma et al. 1997	N=88	Bilateral posterior hypoperfusion (parieto-temporal), N=20	Bilateral posterior hypoperfusion (parieto-temporal), N=57 (probable AD)	HMPAO-SPECT Control group: N=11
Donnemiller et al. 1997	N=13	Temporo-parietal hypoperfusion and occipital hypoperfusion (horseshoe-like pattern), N=7 (probable DLB)	Temporal and/or parietal hypoperfusion, Additional frontal hypoperfusion in 2 patients and occipital hypoperfusion in one patient, N=6 (probable AD)	ECD/HMPAO SPECT No control group
Defebvre et al. 1999	N=60	Diffuse cortical abnormalities, Hypoperfusion mainly in all frontal regions, N=20 (probable DLB)	Temporo-parietal hypoperfusion, more pronounced on the left side, N=20 (probable AD)	HMPAO-SPECT Control group: idiopathic Parkinson disease: N=20
Ischii et al. 1999	N=42	Lower CBF in occipital lobe, well preserved medial temporal perfusion, N=14	Lower CBF in right medial temporal lobe, N=14	IMP-SPECT Control group: N=14
Lobotesis et al. 2001	N=93	Reduced CBF in parietal and temporal regions, Frequent occipital hypoperfusion, N=23	Reduced CBF in parietal and temporal regions, N=50	HMPAO-SPECT Control group: N=20
Pasquier et al. 2002	N=62	Reduced mean perfusion index in occipital regions. Diffuse cortical abnormalities. N=34 (probable DLB)	Reduced mean perfusion index in left medial temporal region, N=28 (probable AD)	ECD-SPECT No control group
Colloby et al. 2002	N=91	Parietal and frontal hypoperfusion, Occipital hypoperfusion, N=23	Parietal and frontal hypoperfusion, Temporo-parietal hypoperfusion, N=48	HMPAO-SPECT Control group: N=20

Table 4. Results of comparative SPECT studies and differences found between DLB and AD

pattern strikingly similar to that encountered in AD (27). An interesting finding of the study was that cortical blood-flow changes in DLB group did not reflect cortical neuropsychological deficits, in contrast to findings in the AD group. All DLB patients, but no AD patients had cognitive decline of subcortical type. It seems reasonable to assume that cortical blood-flow changes in DLB reflects a combination of direct cortical pathology and cortical

deafferentation secondary to subcortical pathology. In summary, the above cited study (27) has contributed relatively very little to the clinical differentiation of DLB and AD, because of similarity of blood-flow deficit pattern. SPECT study with Tc-99m HMPAO performed by Lobotesis et al. has shown significantly reduced rCBF in parietal and temporal regions in both DLB and AD subjects. Besides in the AD group significant reduction in rCBF was

noted in the frontal and medial temporal regions, whereas the DLB group revealed significant reduction in the occipital perfusion. Therefore, those two groups differed only in terms of occipital perfusion (28). Similar patterns of cerebral blood-flow have been observed in the studies reported by Donnemiller et al (29), Pasquier et al (30) and Ishii et al (31). All these studies have reported decreased occipital perfusion along with well preserved medial temporal perfusion.

Colloby et al. have found the frontal and parietal hypoperfusion in both AD and DLB, while temporal perfusion deficits were observed exclusively in AD and parieto-occipital deficits in DLB (32). Different patterns of perfusion were found in both groups: AD and DLB by Defebvre et al. They have demonstrated hypoperfusion in all frontal regions in the DLB group as the most sensitive scintigraphic feature for distinguishing DLB and AD in vivo (33). The decrease in Tc-99m HMPAO uptake could be explained by the high density of cortical LB, observed in the frontal cortex in a few cases(34). Results of comparative SPECT studies and differences found between DLB and AD are presented in Table 4.

The great variations in SPECT study results may be explained by the small number of subjects studied at different clinical stages, differences in the quality of imaging equipment used and methods of data analysis. It is interesting to note that DLB patients did not reveal any difference in mean sub-cortical blood-flow compared to control subjects, and that patients with asymmetrical signs of Parkinsonism did not reveal corresponding left-right sub-cortical blood-flow asymmetries (27). This may be probably due to poor resolution of the current imaging systems and difficulties in measuring Tc-99m HMPAO or ECD uptake in regions of small volume (thalamus and lenticular nucleus), but not the absence of sub-cortical abnormalities.

We have limited experience in this field and would like to share our experience in three illustrative cases of dementia.

Patient No.1:

A 72 years old male, six years from disease onset. Severe dementia (MMSE score: 10), deficiencies in executive functions, semantic fluency and phonological fluency. Clock test was severely impaired. Moderate depression. Accordingly to his wife, patient needed constant support in all self care activities (dressing, eating, moving, toilet etc.). She also informed that his cognitive state at home had oscillated from (sometimes) delirium to state of preserved contact and relatively good orientation. The motor problems (shuffle gait and bradykinesia) started along with memory problems and visual hallucinations. Moderate response to rivastigmine treatment (2x3.0mg) and mild improvement after l-dopa with benserazide (3x250mg). Neurological examination revealed severely stooped posture, bradykinesia, dysarthria and rigidity, Hoehn-Yahr stage: IV, Schwab-England: 40%, UPDRS (II,III,IV): 81. The CT scan of the brain revealed diffuse cortical

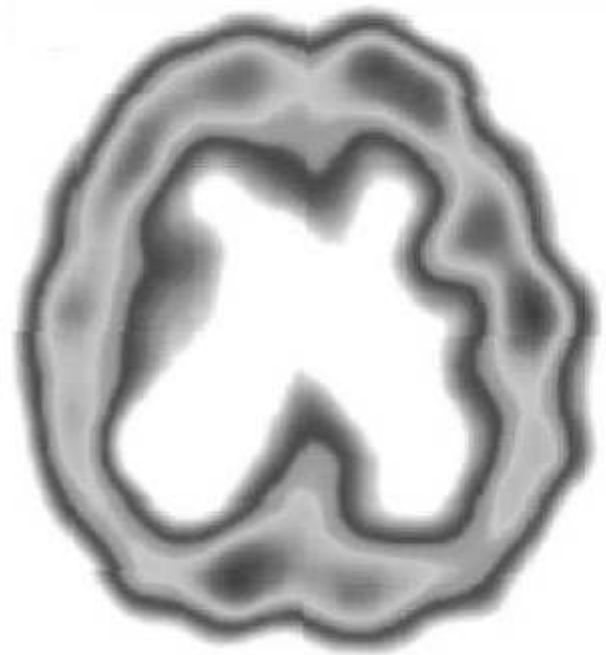


Figure 1. Tc-99m ECD rCBF study on a 72 years old male with severe dementia (MMSE score = 10). Trans-axial section of the brain shows bilateral hypoperfusion of temporal, parietal and occipital lobes.

atrophy, no white matter focal changes. Keeping cerebellar perfusion as the reference point, rCBF SPECT imaging revealed bilateral hypoperfusion of temporal (71%-74%), parietal (73%-76%) and occipital (76%-79%) lobes (Figure-1)

Patient No.2:

A 69 years old female, five years from the disease onset. Mild dementia (MMSE score: 18), moderate deficits in executive functions and semantic and phonological fluency, in spatial test most numerals on the clock face were correct. There were sporadic paragraphic errors in writing, acalculia. Reading was preserved. Memory deficits and depression along with visual hallucinations were present since 2000 and motor problems started insidiously later on. After promazine treatment she was agitated. There was good response to l-dopa with benserazide (4x125mg) and moderate response to rivastigmine (2x3.0mg). Neurological examination revealed left side resting tremor and rigidity, slightly stooped posture and mild bradykinesia. Hoehn-Yahr stage: 2.5, Schwab-England: 70%, UPDRS (II,III,IV) score: 34. MRI study revealed slight dilatation of ventricles and small diffused white matter T2 hyperintensities. Tc-99m ECD rCBF SPECT imaging (Figure-2), with cerebellar perfusion as the reference point revealed hypoperfusion (68-79%) of entire brain, most expressed in temporal (74%-79%), parietal (68-75%) and parieto-occipital (74%-77%) regions. Hypoperfusion of left thalamus, AI=20%.

Patient No.3:

A 74 years old male, 2 years from the disease onset. Severe dementia (MMSE=9) with fluctuations of cognition.



Figure 2. Tc-99m ECD rCBF study on a 69 years old female with mild dementia (MMSE score = 18). Trans-axial section of the brain shows bilateral hypoperfusion of entire brain, most expressed in temporal, parietal and parieto-occipital regions.

Cognitive dysfunction (memory disturbances) had started 2 years ago. Accordingly to his wife, he is unable to take care of himself. He has also spatial problems outside the house.

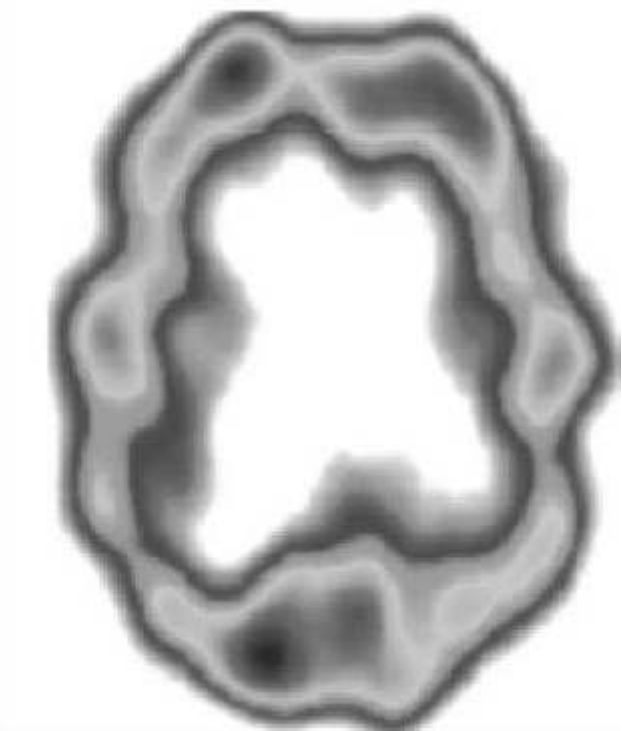


Figure 3. Tc-99m ECD rCBF study on a 74 years old male with severe dementia (MMSE score =9). Trans-axial section of the brain shows predominantly decreased cerebral blood flow within posterior temporal, parietal and parieto-occipital regions.

Verbal learning curve tended to be low and decreased during testing. Executive functions in fluency tests showed moderate deficit. There was very limited understanding, severe alexia, signs of agraphia and acalculia. Repetition of words was not disturbed. He was administered l-dopa with benserazide 3x125 mg with good response and rivastigmine 2x3.0 mg without any improvement or deterioration in the 6 months observation period. Neurological examinations revealed mild bradykinesia, rigidity (P L), stooped posture, retropulsion and hypomimia. Hoehn-Yahr stage: 2, Schwab-England score: 70% and UPDRS (II,III, IV) score: 30. CT scans of brain revealed cortical atrophy (parietal, frontal and temporal). Keeping cerebellar perfusion as the reference point, rCBF SPECT imaging using Tc-99m ECD (Figure-3) revealed pattern of predominantly decreased cerebral blood flow within posterior temporal (74%-76%), parietal (69%-73%) and parieto-occipital (69%-80%) regions. Hypoperfusion of right thalamus AI=13%.

SPECT studies of the dopaminergic system

Loss of dopaminergic cells is accompanied by loss of dopamine transporting system (presynaptic receptors) in DLB. Due to this neuro-pathological phenomenon, dopamine transporter has been used as a surrogate marker for assessing integrity of the nigrostriatal dopaminergic pathways. Cocaine analogues like I-123 (FP-CIT) (DaTSCAN) or I-123-β-CIT have shown selective affinity for the dopamine transporting system.

In a study of sub-cortical dysfunction for distinguishing DLB, PD and AD Walker et al. (5) have examined the integrity of the nigrostriatal metabolism using dopaminergic presynaptic ligand FP-CIT in DLB, AD and PD patient groups. Both DLB and PD patients revealed significantly lower uptake of radioactivity compared to patients with AD and controls in the caudate nucleus and the anterior and posterior putamen. However it has not been possible to distinguish between PD and DLB cases. This was the first study which showed the possibility to detect a clear reduction in striatal dopamine transporter in patients with DLB using FP-CIT SPECT, which might be helpful in differentiating DLB from AD. Similar results were also reported by O'Brien et al (35) and Donnemiller et al (29) with another presynaptic striatal dopamine transporter I-123-β-CIT. Another recent study by Walker et al., with I-123-FP-CIT showed differences between PD and DLB with regard to the pattern of striatal dopaminergic dysfunction (36). DLB patients do not show the characteristic selective degeneration of ventrolateral nigral neurons seen in PD. Several studies reported a more marked and symmetrical Parkinsonian syndrome in DLB compared to PD. Ransmayr et al. have compared Parkinsonian features and loss of striatal dopamine transporter function in patients with DLB and PD matched for age and disease duration with I-123-β-CIT. This study suggests that Parkinsonism evolves largely symmetrically and progresses more rapidly with more severe loss of striatal dopamine transporter function in DLB compared to PD (37). Whether these

results are helpful in the differential diagnosis of DLB and PD needs to be examined in further studies.

As mentioned above dopamine transporter FP-CIT SPECT might be helpful in supporting the diagnosis of DLB in patients with dementia. It has to be stressed that this supportive role of FP-CIT study is of special value when differentiating patients with DLB and AD. One should bear in mind that other dementia syndromes that also involve nigrostriatal pathology, like corticobasal degeneration or fronto-temporal dementia with Parkinsonism may give an abnormal FP-CIT SPECT uptake (5).

Another study with I-123 IBZM radiopharmaceutical for imaging of post-synaptic dopamine D2 receptor uptake has revealed changes in striatum compared to AD and control subjects (38). In PD, there is upregulation of post-synaptic D2 receptors in the putamen, with no change in the caudate (39), so the caudate/putamen ratio is reduced. In contrast, AD is not associated with significant changes in dopamine metabolism. Therefore patients with DLB show the same deregulation of striatal dopamine neurotransmission as is seen in early PD, but not in AD.

Positron Emission Tomography (PET) studies

One of the first studies with F-18 Fluoro-deoxyglucose (FDG) PET reported six demented individuals with pathologically verified diffuse Lewy bodies disease. This study provided evidence of diffuse cerebral hypometabolism (frontal, temporal and parietal) in both pure DLB (3 patients) and combined DLB-AD (3 patients) with more pronounced decline in parietal cortex activity, sparing the primary somatomotor cortex and subcortical structures. Unlike AD occipital hypometabolism has been reported in both occipital association cortex and primary visual cortex, which could be related to visual hallucinations observed in DLB (40). However a few pathological studies have shown the sparing of the occipital lobe (41,42). Similar results have also been published by Imamura et al. with accompanying hypoperfusion in cerebellar hemispheres (43). Minoshima et al. in their study with autopsy confirmed cases observed significant metabolic reduction involving parietotemporal region, posterior cingulate and frontal associative cortex. Only DLB patients showed significant metabolic reduction in the occipital cortex, particularly in the primary visual cortex, which distinguished DLB from AD with 90% sensitivity and 80% specificity (44). On the other hand entirely different results have been reported by Mirzaei et al in FDG-PET study showing diffuse glucose hypometabolism in the entire cerebral cortex with relative sparing of the primary sensory-motor cortex in all patients. The author claimed this to be a typical pattern for DLB distinct from AD (45).

One of the recent FDG-PET studies from Gilman et al. (46) has shown significantly lower regional cerebral metabolic rates for glucose (rCMRglc) for visual cortex (Brodmann areas 17, 18, and 19) in the DLB than the AD group and no differences for other regions commonly affected in AD,

including posterior cingulate superior parietal lobe, lateral temporal lobe and the prefrontal region. An interesting comparative study of DLB patients with and without Parkinsonism in a group of patients suffering from AD has shown that medial and lateral occipital regional cerebral metabolic rate of glucose (rCMRglc) was significantly lower in the DLB patients without Parkinsonism than in the AD group and that there were no significant differences in occipital metabolic rates between the DLB group with and without Parkinsonism (47). It might suggest that lower occipital rCMRglc could be the marker for DLB, independent of clinical symptoms of Parkinsonism. In summary, most of the above cited studies, along with observations of other groups (48,49,50,) have shown more or less identical results. A pattern of occipital hypometabolism seems to be an informative diagnostic aid to distinguish DLB from AD. Comparison of results of PET studies in DLB and AD is presented in Table 5.

Positron Emission Tomography (PET) studies of dopaminergic system

To our knowledge there is only one study on DLB done with F-18 fluorodopa PET, analyzing the nigrostriatal dopaminergic function for distinguishing DLB and AD. It shows that patients with DLB and extrapyramidal signs which are responsive to L-dopa have significantly reduced uptake of F-18 fluorodopa in the putamen and the caudate nuclei (51). This study extends the previous observation by Donnemiller et al., which has reported significantly reduced striatal/cerebellar ratio of I-123 - β -CIT binding in patients with DLB compared to AD (29).

PET and SPECT studies of other neurotransmitter systems

DLB is associated with profound acetylcholinergic deficits as compared to AD, which has lower level of choline acetyltransferase activity in the neocortex (21, 52-54). With the newly developed radiolabeled lipophilic acetylcholine analogue, N- 11 C-methyl-4-piperidyl-acetate (11 C-MP4A) it is possible to measure regional acetylcholine esterase activity in brain by PET in vivo. There are only few studies with MP4A in patients with DLB. One study by Herholz et al. conducted on a very small number of demented subjects has shown that the activity of acetylcholine esterase in one patient with DLB was in the lower range compared to patients with AD (55). This acetylcholinergic deficit may explain why cholinergic therapy is so effective in patients with DLB.

Extracranial radionuclide studies

As mentioned above LB may be found in the peripheral nervous system, for example in the cardiac plexus. Scintigraphy with I-123 metaiodobenzylguanidine (I-123 MIBG) enables the quantification of postganglionic sympathetic cardiac innervation. The heart/mediastinum ratio (H/M) of I-123 MIBG uptake in patients with AD was indistinguishable from that in the control group and H/M ratio in all patients with DLB was significantly lower than in patients with AD and control subjects (15). Similar

References	No of pts studied	PET Results in DLB and N (No. of patients studied)	PET Results in AD and N (No. of patients studied)	Comments
Albin et al 1996	N=6	Diffuse cerebral hypometabolism particularly pronounced in association cortex with relative sparing of subcortical structures and primary somatomotor cortex. Hypometabolism in occipital association and primary visual cortex. N=6 (3 patients with pure DLB and 3 combined DLB and AD pathology)		FDG-PET No control group
Imamura et al. 1997	N=38	Decrease of rCMRglc in temporo-parieto-occipital association cortex and cerebellar hemispheres. N=19	Decrease of rCMRglc in medial temporal and cingulate cortex N=19	FDG-PET No control group
Higuchi et al. 2000	N=38	Most pronounced hypometablism in visual association cortex N=7	N=21	FDG-PET Control group N=10
Minoshima et al. 2001	N=21	Significant hypometabolism in parietotemporal and frontal association and posterior cingulate cortex. Hypometabolism in occipital (particularly primary visual) cortex. N=11 (4 pure DLB and 7 Lewy body variant of AD with autopsy confirmation)	Significant hypometabolism in parieto-temporal and frontal association and posterior cingulate cortex N=10 (autopsy confirmed pure AD)	FDG-PET No control group
Okamura et al. 2001	N=28	Widespread hypometabolism particularly pronounced in occipital cortex (primary in visual association cortex). N=7	N=11	FDG-PET Control group N=10
Imamura et al. 2001	N=22	Significant hypometabolism of occipital cortex. No significant differences in occipital rates between DLB with and without parkinsonism. N=15 (7 patients without and 7 with parkinsonism)	N=7 (patients with AD without parkinsonism)	FDG-PET No control group
Marzaei et al. 2003	N=7	Diffuse Glc hypometabolism in the entire cerebral cortex with relative sparing of primary sensory motor cortex. N=7		FDG-PET No control group
Gilman et al. 2005	N=64	Lower rCMRglc for visual cortex than in AD group. N=20	N=25	FDG-PET Control group N=19

Table 5. Comparison of the results of PET studies in DLB and AD.

results were also reported by Yoshita and colleagues (56). In another study with MIBG the authors studied the possible association between heart disease and presence of LB in the cardiac plexus. The results showed that heart disease and arrhythmia complications were more frequent in cases with Lewy body disease than in those with Parkinson syndrome (cases with Parkinsonism but without intracranial LB) and that LB were more frequently found in extracranial organs, especially in the sinoatrial nodal ganglion, in DLB (57).

Conclusions

The characteristic pattern of metabolic and perfusion changes in DLB have been shown in most of the studies. Biparietal hypoperfusion – greater in DLB when compared to AD, occipital hypoperfusion in DLB (whereas hardly normal occipital perfusion in AD) and relative preservation of temporal lobe perfusion seem to be helpful to differentiate the two entities (28, 29, 31, 32). Most studies on dopamine transport system in DLB have shown reduction in striatal uptake when compared with AD patients, but the differentiation from PD using this method has not been possible (5,29,35). Until now, no functional imaging method has been applied as a diagnostic tool in DLB, especially in terms of definition and classification. Diagnosis of DLB during life has to be based on diagnostic criteria proposed by Newcastle Consortium in 1996 and remain based on clinical symptoms and signs. Nevertheless this review of literature reveals the clinical utility of functional imaging and its important contributions to the understanding of pathogenesis, as well as diagnosis and treatment of dementia.

References

- Rahkonen T, Eloniemi-Sulkava U, Rissanen S, Vatanen A, Viramo P, Sulkava R. Dementia with Lewy bodies according to the consensus criteria in a general population aged 75 years or older. *J Neurol Neurosurg Psychiatry* 2003; 74: 720-724.
- Ransmayr G, Wenning GK, Seppi K, Jellinger K, Poewe W. Dementia with Lewy bodies. *Nervenarzt* 2000; 71: 929-35.
- Burn DJ, Mosimann UP, McKeith IG. Clinical Diagnosis of dementia with Lewy bodies. In: Litvan I. eds: *Atypical Parkinsonian Disorders*. Humana Press, Totowa, New Jersey 2005; 361-373
- McKeith I, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathological diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology* 1996; 47: 1113-1124.
- Walker Z, Costa DC, Walker RW, et al. Differentiation of dementia with Lewy bodies from Alzheimer's disease using a dopaminergic presynaptic ligand. *J Neurol Neurosurg Psychiatry* 2002; 73: 134-140.
- McKeith I, Fairbairn A, Perry R, Thompson P, Perry E. Neuroleptic sensitivity in patients with senile dementia of lewy body type. *BMJ* 1992; 305: 673-678.
- Ballard C, Grace J, McKeith I, Holmes C. Neuroleptic sensitivity in dementia with Lewy bodies and Alzheimer's disease. *Lancet* 1998; 351: 1032-1033.
- Lewy F. Zur pathologischen Anatomie der Paralysis agitans. *Dtsch Z Nervenheilkd* 1913; 50: 50-55.
- Spillantini MG, Schmidt ML, Lee VM, Trojanowski LQ, Jakes R, Goedert M. Alpha-synuclein in Lewy bodies. *Nature* 1997; 388: 839-840.
- Okazaki H, Lipkin LE, Aronson SM. Diffuse intracytoplasmic ganglionic inclusions (Lewy type) associated with progressive dementia and quadriplegia in flexion. *J Neuropathol Exp Neurol* 1961; 20: 237-244.
- Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992; 55: 181-184.
- Wakabayashi K, Takahashi H, Ohama E, Ikuta F. Parkinson's disease: an immunohistochemical study of Lewy body-containing neurons in the enteric nervous system. *Acta Neuropathol (Berl)* 1990; 79: 581-583.
- Wakabayashi K, Takahashi H. Neuropathology of autonomic nervous system in Parkinson's disease. *Eur Neurol* 1997; 38 Suppl 2: 2-7.
- Hague K, Lento P, Morgello S, Caro S, Kaufmann H. The distribution of Lewy bodies in pure autonomic failure: autopsy findings and review of the literature. *Acta Neuropathol (Berl)* 1997; 94: 192-196.
- Watanabe H, Ieda T, Katayama T, et al. Cardiac (123)I-meta-iodobenzylguanidine (MIBG) uptake in dementia with Lewy bodies: comparison with Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2001; 70: 781-783.
- Kosaka K, Yoshimura M, Ikeda K, Budka H. Diffuse type of Lewy body disease: progressive dementia with abundant cortical Lewy bodies and senile changes of varying degree—a new disease? *Clin Neuropathol* 1984; 3: 185-192.
- Kosaka K. Diffuse Lewy body disease in Japan. *J Neurol* 1990; 237: 197-204.
- Perry RH, Irving D, Blessed G, Fairbairn A, Perry EK. Senile dementia of Lewy body type. A clinically and neuropathologically distinct form of Lewy body dementia in the elderly. *J Neurol Sci* 1990; 95: 119-139.
- Galasko D, Katzman R, Salmon DP, Hansen L. Clinical and neuropathological findings in Lewy body dementias. *Brain Cogn* 1996; 31: 166-175.
- Mosimann UP, McKeith IG. Dementia with lewy bodies—diagnosis and treatment. *Schweiz Med Wochenschr* 2003; 133: 131-142.
- Tiraboschi P, Hansen LA, Alford M, et al. Cholinergic dysfunction in diseases with Lewy bodies. *Neurology*

- 2000; 54: 407-411.
22. Piggott MA, Marshall EF, Thomas N, et al. Striatal dopaminergic markers in dementia with Lewy bodies, Alzheimer's and Parkinson's diseases: rostrocaudal distribution. *Brain* 1999; 122: 1449-1468.
 23. Barber R, Ballard C, McKeith IG, Gholkar A, O'Brien JT. MRI volumetric study of dementia with Lewy bodies: a comparison with AD and vascular dementia. *Neurology* 2000; 54: 1304-1309.
 24. Barber R, McKeith I, Ballard C, O'Brien J. Volumetric MRI study of the caudate nucleus in patients with dementia with Lewy bodies, Alzheimer's disease, and vascular dementia. *J Neurol Neurosurg Psychiatry* 2002; 72: 406-407.
 25. Barber R, Gholkar A, Scheltens P, Ballard C, McKeith IG, O'Brien JT. Medial temporal lobe atrophy on MRI in dementia with Lewy bodies. *Neurology* 1999; 52: 1153-1158.
 26. Barber R, Scheltens P, Gholkar A, et al. White matter lesions on magnetic resonance imaging in dementia with Lewy bodies, Alzheimer's disease, vascular dementia, and normal aging. *J Neurol Neurosurg Psychiatry* 1999; 67: 66-72.
 27. Varma AR, Talbot PR, Snowden JS, Lloyd JJ, Testa HJ, Neary D. A 99mTc-HMPAO single-photon emission computed tomography study of Lewy body disease. *J Neurol* 1997; 244: 349-59.
 28. Lobotesis K, Fenwick JD, Phipps A, et al. Occipital hypoperfusion on SPECT in dementia with Lewy bodies but not AD. *Neurology* 2001; 56: 643-649.
 29. Donnemiller E, Heilmann J, Wenning GK, et al. Brain perfusion scintigraphy with 99mTc-HMPAO or 99mTc-ECD and 123I-beta-CIT single-photon emission tomography in dementia of the Alzheimer-type and diffuse Lewy body disease. *Eur J Nucl Med* 1997; 24: 320-325.
 30. Pasquier J, Michel BF, Brenot-Rossi I, Hassan-Sebbag N, Sauvan R, Gastaut JL. Value of (99m)Tc-ECD SPET for the diagnosis of dementia with Lewy bodies. *Eur J Nucl Med Mol Imaging* 2002; 29: 1342-1348.
 31. Ishii K, Yamaji S, Kitagaki H, Imamura T, Hirono N, Mori E. Regional cerebral blood flow difference between dementia with Lewy bodies and AD. *Neurology* 1999; 53: 413-416.
 32. Colloby SJ, Fenwick JD, Williams ED et al. A comparison of (99m)Tc-HMPAO SPET changes in dementia with Lewy bodies and Alzheimer's disease using statistical parametric mapping. *Eur J Nucl Med Mol Imaging* 2002; 29: 615-622.
 33. Defebvre LJ, Leduc V, Duhamel A, et al. Technetium HMPAO SPECT study in dementia with Lewy bodies, Alzheimer's disease and idiopathic Parkinson's disease. *J Nucl Med* 1999; 40: 956-962.
 34. Forstl H, Burns A, Luthert P, Cairns N, Levy R. The Lewy-body variant of Alzheimer's disease. Clinical and pathological findings. *Br J Psychiatry* 1993; 162: 385-392.
 35. O'Brien JT, Colloby S, Fenwick J, et al. Dopamine transporter loss visualized with FP-CIT SPECT in the differential diagnosis of dementia with Lewy bodies. *Arch Neurol* 2004; 61: 919-925.
 36. Walker Z, Costa DC, Walker RW et al. Striatal dopamine transporter in dementia with Lewy bodies and Parkinson disease: a comparison. *Neurology* 2004; 62: 1568-1572.
 37. Ransmayr G, Seppi K, Donnemiller E, et al. Striatal dopamine transporter function in dementia with Lewy bodies and Parkinson's disease. *Eur J Nucl Med* 2001; 28: 1523-1528.
 38. Walker Z, Costa DC, Janssen AG, Walker RW, Livingstone G, Katona CL. Dementia with lewy bodies: a study of post-synaptic dopaminergic receptors with iodine-123 iodobenzamide single-photon emission tomography. *Eur J Nucl Med* 1997; 24: 609-614.
 39. Brooks DJ. Functional imaging in relation to parkinsonian syndromes. *J Neurol Sci* 1993; 115: 1-17.
 40. Albin RL, Minoshima S, D'Amato CJ, Frey KA, Kuhl DA, Sima AA. Fluoro-deoxyglucose positron emission tomography in diffuse Lewy body disease. *Neurology* 1996; 47: 462-466.
 41. Gibb WRG, Esiri MM, Lees AJ. Clinical and pathological features of diffuse cortical Lewy body disease (Lewy body dementia). *Brain* 1985; 110: 1131-1153.
 42. McKeith IG, Fairbairn AF, Perry RH, Thompson P. The clinical diagnosis and misdiagnosis of senile dementia of Lewy body type (SDLT). *Br J Psychiatry* 1994; 165: 324-332.
 43. Imamura T, Ishii K, Sasaki M, et al. Regional cerebral glucose metabolism in dementia with Lewy bodies and Alzheimer's disease: a comparative study using positron emission tomography. *Neurosci Lett* 1997; 235: 49-52.
 44. Minoshima S, Foster NL, Sima AA, Frey KA, Albin RL, Kuhl DE. Alzheimer's disease versus dementia with Lewy bodies: cerebral metabolic distinction with autopsy confirmation. *Ann Neurol* 2001; 50: 358-365.
 45. Mirzaei S, Rodrigues M, Koehn H, Knoll P, Bruecke T. Metabolic impairment of brain metabolism in patients with Lewy body dementia. *Eur J Nucl Med* 2003; 10: 573-575.
 46. Gilman S, Koeppe RA, Little R, et al. Differentiation of Alzheimer's disease from dementia with Lewy bodies utilizing positron emission tomography with [18F]fluorodeoxyglucose and neuropsychological testing. *Neurol* 2005; 191(Suppl 1): 95-103.
 47. Imamura T, Ishii K, Hirono N, et al. Occipital glucose metabolism in dementia with lewy bodies with and without Parkinsonism: a study using positron emission tomography. *Dement Geriatr Cogn Disord* 2001; 12: 194-197.

48. Higuchi M, Tashiro M, Arai H, et al. Glucose hypometabolism and neuropathological correlates in brains of dementia with Lewy bodies. *Exp Neurol* 2000; 162: 247-256.
49. Okamura N, Arai H, Higuchi M, et al. [¹⁸F]FDG-PET study in dementia with Lewy bodies and Alzheimer's disease. *Prog Neuropsychopharmacol Biol Psychiatry* 2001; 25: 447-456.
50. Ishii K, Hosaka K, Mori T, Mori E. Comparison of FDG-PET and IMP-SPECT in patients with dementia with Lewy bodies. *Ann Nucl Med* 2004; 18: 447-451.
51. Hu XS, Okamura N, Arai H, et al. ¹⁸F-fluorodopa PET study of striatal dopamine uptake in the diagnosis of dementia with Lewy bodies. *Neurology* 2000; 55: 1575-1577.
52. Perry EK, Haroutunian V, Davis KL, et al. Neocortical cholinergic activities differentiate Lewy body dementia from classical Alzheimer's disease. *Neuroreport* 1994; 5: 747-749.
53. Perry EK, Marshall E, Kerwin J, et al. Evidence of a monoaminergic-cholinergic imbalance related to visual hallucinations in Lewy body dementia. *J Neurochem* 1990; 55: 1454-1456.
54. Shiozaki K, Iseki E, Uchiyama H, et al. Alterations of muscarinic acetylcholine receptor subtypes in diffuse lewy body disease: relation to Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 1999; 67: 209-213.
55. Herholz K, Bauer B, Wienhard K, et al. In-vivo measurements of regional acetylcholine esterase activity in degenerative dementia: comparison with blood flow and glucose metabolism. *J Neural Transm* 2000; 107: 1457-1468.
56. Yoshita M, Taki J, Yamada M. A clinical role for [(123)I]MIBG myocardial scintigraphy in the distinction between dementia of the Alzheimer's-type and dementia with Lewy bodies. *J Neurol Neurosurg Psychiatry* 2001; 71: 583-588.
57. Okada Y, Ito Y, Aida J, Yasuhara M, Ohkawa S, Hirokawa K. Lewy bodies in the sinoatrial nodal ganglion: clinicopathological studies. *Pathol Int* 2004; 54: 682-687.