Striatal Monoamine Terminals in Lewy Body Dementia and Alzheimer's Disease

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We used positron emission tomography (PET) with (+)-[^{11}C]dihydrotetrabenazine ([+]-[^{11}C]DTBZ) to examine striatal monoaminergic presynaptic terminal density in 20 patients with dementia with Lewy bodies (DLB), 25 with Alzheimer's disease (AD), and 19 normal elderly controls. Six DLB patients developed parkinsonism at least 1 year before dementia (DLB/PD) and 14 developed dementia before parkinsonism or at about the same time (DLB/AD). Striatal mean binding potential was decreased by 62 to 77% in the DLB/PD group and 45 to 67% in the DLB/AD compared to AD and control. Binding was lower in the DLB/PD group than the DLB/AD, but the differences reached only marginal significance in the caudate nucleus. No differences were found between AD and control groups though a few AD patients had binding values below the range of the controls. Subsequent neuropathological examination in one AD patient revealed both AD and DLB changes despite the absence of clinical parkinsonism. Both DLB groups had an anterior to posterior binding deficit gradient relative to controls, largest in posterior putamen, smaller in anterior putamen, smallest in caudate nucleus. The DLB/AD group showed significant binding asymmetry only in posterior putamen. We conclude that PET with (+)-[^{11}C]DTBZ differentiates DLB from AD, and decreased binding in AD may indicate subclinical DLB pathology in addition to AD pathology.

Dementia with Lewy bodies (DLBs) may be the second most frequent cause of dementia in the elderly, accounting for 15 to 25% of cases.[1] Alzheimer's disease (AD) is the most frequent cause and is responsible for 50 to 60% of dementia cases in the elderly. The neuropathological features of DLB include widespread neuronal degeneration with deposition of Lewy bodies and Lewy neurites, which contain α-synuclein as a major filamentous component.[2] Substantial neuronal loss occurs in the substantia nigra and nigrostriatal projections are decreased. Many cases of DLB show concomitant neuropathological changes of AD.[1,3] Despite this overlap, DLB appears to be a distinctive clinicopathological entity characterized as an α-synucleinopathy along with idiopathic Parkinson's disease (PD) and multiple system atrophy.[1,4] Lewy bodies contain other abnormal proteins in addition to α-synuclein, notably parkin.[5]

The central features of DLB include parkinsonism with a progressive dementia, and the latter includes deficits in memory, attention, language, psychomotor performance, executive functioning, and visuospatial and visuoconstructive abilities.[6] Perceptual and affective disturbances appear more frequently in DLB than AD and consist of recurrent visual hallucinations,[7,8] delusions,[8] depression,[7] and agitation.[9] Sensitivity to neuroleptic drugs is prominent.[10] Both bradykinesia and rigidity occur frequently,[8] but resting tremor is rare.[8,10] The parkinsonian features in DLB are more symmetrical than in PD.[10] Consensus criteria have been developed for the clinical diagnosis of DLB,[11] but several prospective and retrospective studies of these criteria generally have shown limited accuracy. With neuropathological findings as the gold standard,[12–17] these studies have shown the sensitivity of the criteria to range from 31%[17] to 83%[16] and the specificity from 64%[15] to 100%.[17]

Because disease-modifying treatments soon may become available for neurodegenerative dementias, early diagnosis becomes increasingly important. To this end, we initiated a positron emission tomography (PET) study in DLB and AD using (+)-[^{11}C]dihydrotetrabenazine ([+]-[^{11}C]DTBZ) to examine nigrostriatal projections. (+)-[^{11}C]DTBZ binds to the monoaminergic vesicular transporter type 2 and is useful for evaluating nigrostriatal projections. The study was designed to detect

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differences in biochemistry, relate the differences to clinical presentation, and determine whether this ligand would be helpful in differentiating cases, particularly in the early stages. We report here the results of studies with PET and (+)-[^{11}C]DTBZ in patients meeting consensus for DLB,[11] patients meeting National Institute of Neurological Communicative Disorders and Stroke Alzheimer's Disease and Related Disorders Association (NINDS-ADRDA) criteria for AD,[18] and a group of elderly normal control subjects. We selected patients with advanced disorders with the intention of examining patients in the early stages of these disorders in a later study.

Subjects and Methods

Subject Selection

The institutional review board of the University of Michigan approved the investigation. We obtained informed consent from all participants or their caregivers. We studied 64 subjects, including 25 with AD aged 69.3 ± 9.1 years (mean ± standard deviation; range, 52–85 years, 7 men and 18 women); 20 with DLB aged 72.8 ± 7.2 years (range, 54–81 years; 15 men and 5 women); and 19 normal elderly controls aged 69.1 ± 7.6 years (range, 55–86 years; 10 men and 9 women). We used NINCDS-ADRDA criteria for the diagnosis of AD[18] and consensus criteria[11] for the diagnosis of probable DLB. We divided the DLB cases into two groups, six who developed parkinsonian features at least 1 year before dementia appeared (DLB/PD) and 14 who developed dementia before parkinsonism or at about the same time (DLB/AD).

Subject Evaluations

All subjects were evaluated with general physical and neurological examinations, neuropsychological evaluations, magnetic resonance (MR) scans, PET scans, and appropriate laboratory studies to ensure the accuracy of the clinical diagnosis. None of the subjects had a history of disturbances in consciousness, serious head injury, stroke, or abuse of alcohol or drugs. All subjects had a modified Hachinski score of less than 4[19] and no focal abnormality in computed tomography or MR scan except for "bright spots" or mild generalized atrophy. All subjects had adequate hearing and visual acuity to complete the studies, including neuropsychological evaluations. In the patient groups, there were no systemic diseases or other brain diseases that could account for their neurological deficits. We evaluated all medications that the patients were taking and ensured that cognitive impairment persisted after withdrawal of medications that might impair cognition. If depressive features were found, we made certain that the dementia did not reverse with antidepressants. Thirteen DLB patients were taking carbidopa/L-dopa, but this medication has no effect on binding of (+)-[^{11}C]DTBZ. The laboratory studies included a complete blood count, sedimentation rate, chemical profile, urinalysis, serological test for syphilis, thyroid studies, and serum levels of vitamin B_{12} and folic acid. These studies were normal or judged to be clinically insignificant. Although (+)-[^{11}C]DTBZ binding is not known to be altered by medications, medications that

might influence dopaminergic presynaptic neurons were discontinued 4 weeks before the PET study.

Neuropsychological Testing

We assessed general mental status and orientation with the Mini-Mental State Examination (MMSE),[20] attention with the Digit Span test,[21] language with the Multilingual Aphasia Examination Visual Naming Test,[22] visual-spatial ability with the Visual Form Discrimination Test,[23] memory with the Hopkins Verbal Learning Test–Revised,[24] and family ratings of general motor ability with the motor subscale of the Inventory of Psychic and Somatic Complaints–Elderly.[25]

Positron Emission Tomography Imaging

We injected 18 ± 1.8mCi of (+)-[^{11}C]DTBZ to measure the density of striatal monoaminergic terminals.[26,27] This stereospecific ligand has a high affinity (K_D = 1 nM) for the vesicular monoamine transporter type 2 (VMAT2) site. The radiotracer was administered as a partial bolus (55% of the injected dose) followed by continuous infusion (the remaining 45%) over the duration of the PET study. In the course of this investigation, we replaced our PET scanner. Consequently, we studied 25 subjects with a Siemens/CTI ECAT Exact-47 scanner (10 DLB patients, 9 AD patients, and 6 normal controls) and 39 subjects with a Siemens/CTI ECAT Exact HR+ scanner (10 DLB patients, 16 AD patients, and 13 normal controls). All scans were performed in three-dimensional mode with the interplane septa retracted. Measured attenuation correction was performed from a 6 to 10-minute-duration two-dimensional transmission scan followed by segmentation and reprojection. Scatter correction also was performed on all scans. After Fourier rebinning (FORE) of the three-dimensional data into two-dimensional data sets, scans were reconstructed with smoothing parameters selected that provided images for both scanners with in-plane and axial resolution of approximately 8.5mm full-width at half-maximum. Statistical checks showed that any residual scanner effects were negligible and had no substantive impact on any of the results or conclusions.

Data Analysis

The continuous infusion protocol for [^{11}C]DTBZ administration allows an equilibrium analysis to be performed.[27] An index of the density of striatal presynaptic monoaminergic terminals was estimated as the distribution volume ratio (DVR) relative to occipital cortex, or equivalently as the normalized specific binding density called the binding potential (BP), which equals DVR-1. The occipital cortex served as a reference region containing negligible specific binding, thus reflecting the distribution volume of free plus nonspecifically bound [^{11}C]DTBZ. DVR was measured in the caudate nucleus and in the anterior and posterior putamen using three-dimensional rectangular volumes of interest (VOIs) of 4.5 × 9 × 4.5mm. VOIs were centered on the areas of greatest DVR in the caudate nucleus, then moved successively 11 and 20mm posteriorly, and recentered on the area of greatest DVR in the anterior and posterior putamen, respectively. Striatal binding values were calculated as the simple average of values in both hemispheres for each of the three regions. Percentage of asym-

metry of binding was measured in each of the three striatal regions as the absolute difference in regional BP values in the right and left hemispheres divided by the mean of the two sides. Differences between patient and control mean BP values for striatal $(+)$-$[^{11}C]$DTBZ binding were examined by analysis of variance, and t tests were used for pairwise comparisons. To adjust for age and sex, we included these variables as covariates in regression models of the striatal binding values on subject group. For regressions of asymmetry of binding, cases were weighted by their striatal binding values to allow for nonconstant variance.

Results

Subject Group Comparisons
The four groups did not differ in mean age ($p = 0.41$), but the AD group contained a higher proportion of women than the other groups (Table 1). Symptom duration was longer in the DLB/PD group than the other two patient groups. There was no difference between patient groups in either mean MMSE scores (see Table 1) or in other tests that sampled major categories of cognitive functions, including attention, language, visual-spatial ability, and memory ($p > 0.35$). The only difference found was in motor ability (see Table 1).

Striatal $(+)$-$[^{11}C]$Dihydrotetrabenazine Binding
The Figure contains the binding potential values for striatal $(+)$-$[^{11}C]$DTBZ binding of normal control subjects, AD patients, and DLB/AD and DLB/PD patients for the caudate nucleus, anterior putamen, and posterior putamen. The illustration shows a broader range of values in all three structures for the AD group in comparison with the normal control group, but no other difference. In contrast, values for both DLB groups are appreciably lower than the other two

groups, with the DLB/PD generally lower than the DLB/AD group. Only a few DLB cases show overlap with either of the other groups, and no overlap occurs between the DLB and normal control groups in either anterior or posterior putamen.

Table 2 contains the age- and sex-adjusted mean and raw standard deviation of BP by striatal structure. In the caudate nucleus, anterior putamen, and posterior putamen, mean binding potential is decreased by 62 to 77% in the DLB/PD group and by 45 to 67% in the DLB/AD group compared with AD and control groups ($p < 0.001$ in all cases). There is a marginal difference between DLB/AD and DLB/PD groups in the caudate nucleus only and no difference between control and AD groups. Table 2 shows a gradient of BP decline in both DLB groups relative to the control group across individual components of the striatum, with the greatest decline in the posterior putamen (-70%), a smaller decline in the anterior putamen (-64%), and the smallest decline, though still substantial, in the caudate nucleus (-50%). These declines in the DLB groups relative to the control and AD groups are significant in all three striatal structures ($p < 0.0001$).

Table 3 shows the age- and sex-adjusted weighted mean and raw standard deviation of relative asymmetry of BP for normal control, AD, and DLB groups by striatal structure. There are no significant differences between groups for the caudate nucleus and anterior putamen, but for the posterior putamen the DLB/AD group has a higher relative asymmetry than the control and AD groups ($p < 0.03$).

Autopsy Verification of Diagnosis
Three patients died between 18 and 40 months after study, including one in the DLB/AD group and two in

Table 1. Subject Characteristics

Characteristic	NC (n = 19)	AD (n = 25)	DLB/AD (N = 14)	DLB/PD (n = 6)
Sex (M:F)	10:9	7:18[a]	11:3	4:2
Age (yr) (range)	69.1 ± 7.6 (55–86)	69.3 ± 9.1 (52–85)	73.4 ± 5.1 (65–80)	71.5 ± 11.2 (54–81)
MMSE (range)	29 ± 1 (26–30)	15 ± 7 (2–27)	17 ± 6 (8–29)	18 ± 9 (6–26)
Symptom duration (yr)	Not applicable	5 ± 3 (1–13)	4 ± 2 (2–7)	8 ± 3[b] (5–13)
Motor functioning	Not applicable	3.3 ± 3.7 (0–12)	6.5 ± 3.0[c,d] (2–10)	12.7 ± 3.1[c,e] (10–16)

Data include mean ± standard deviation and range.

[1]Motor function established from family ratings of general motor ability with the motor subscale of the Inventory of Psychic and Somatic Complaints–Elderly.

[a]Larger proportion of women than men in this group than the other groups ($p < 0.005$).
[b]Longer symptom duration in DLB/PD than in the other groups ($p < 0.01$).
[c]Greater impairment in DLB/AD than in AD ($p = 0.02$).
[d]Greater impairment in DLB/PD than in DLB/AD ($p = 0.009$)
[e]Greater impairment in DLB/PD than in AD ($p < 0.0001$).

NC = normal control; AD = Alzheimer's disease; DLB/AD = patients with a diagnosis of dementia with Lewy bodies who developed parkinsonian symptoms simultaneously with or after the onset of dementia; DLB/PD = patients with a diagnosis of dementia with Lewy bodies who developed parkinsonian symptoms at least 1 year before dementia; MMSE = Mini-Mental State Examination.
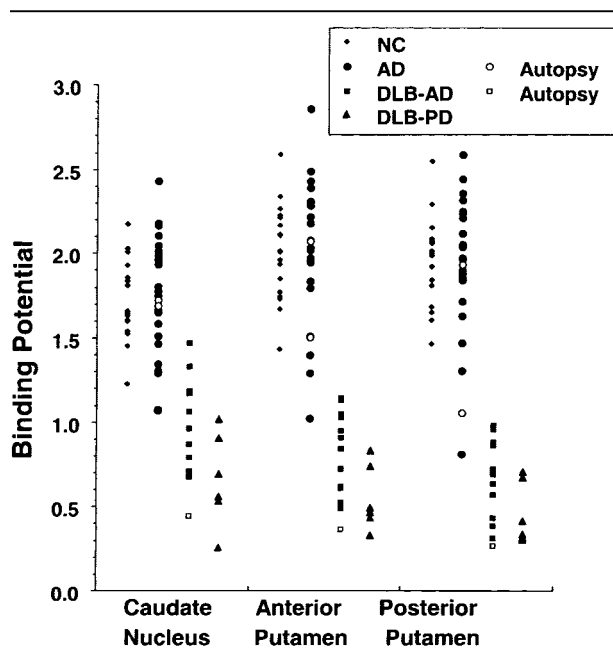
Fig. Binding potential values for striatal (+)-[¹¹C]DTBZ binding of normal control (NC) subjects, patients with Alzheimer's disease (AD), patients with a diagnosis of dementia with Lewy bodies who developed parkinsonian symptoms at least 1 year before dementia (DLB/PD), and patients with a diagnosis of dementia with Lewy bodies who developed parkinsonian symptoms simultaneously with or after the onset of dementia (DLB/AD). Binding potential values are shown for the caudate nucleus, anterior putamen, and posterior putamen. Open symbols indicate the three patients who later came to postmortem examination. The lower of the two open symbols in the AD columns indicates the patient who had neuropathological changes of both AD and DLB.

the AD group. At neuropathological examination, the DLB/AD patient had changes typical of DLB without evidence of AD. In this patient, the BP value was the second lowest of the DLB group in both the caudate nucleus and anterior putamen, and the lowest of the group in the posterior putamen (see Fig). One of the

AD patients had neuropathological changes characteristic of AD without evidence of DLB, and the BP values in this case were approximately in the middle of the AD group for all three striatal structures. The second AD patient had neuropathological findings typical of both AD and DLB, and the BP value was nearly normal in the caudate nucleus (11th lowest of 25) but was fourth lowest in the anterior putamen, and second lowest in the posterior putamen (see Fig). This patient showed no clinical evidence of parkinsonism at the time of study and died 18 months after participating. The patient was examined twice between the time of study and the time of death, and at the second examination 3 months before death the parkinsonian features of mild bradykinesia of face and body with mild rigidity of the limbs were found for the first time.

Discussion

This investigation disclosed significantly decreased striatal binding of (+)-[¹¹C]DTBZ in DLB/AD and DLB/PD patients as compared with both AD and normal control subjects and no difference between the latter two groups. Binding was significantly decreased in all three striatal structures of both DLB groups, with the largest decreases in the posterior putamen and progressively smaller decreases in the anterior putamen and caudate nucleus, respectively. Binding was marginally lower in the DLB/PD than in the DLB/AD group, with a significant difference only in the caudate nucleus. Significantly higher binding asymmetry between the two hemispheres was found for the DLB/AD group as compared with the other groups in the posterior putamen, but no group differences were found in the caudate nucleus or anterior putamen. The mean asymmetry values between the DLB/AD and DLB/PD groups were similar and the different significance values most likely reflect lesser power in the DLB/PD group because of fewer cases. Greater binding asymmetry has been reported in Parkinson's disease than in the present DLB cases.[28,29] Parkinson's disease characteris-

Table 2. Mean and Standard Deviation of the Binding Potential for Each Striatal Structure after Adjustment for the Covariates of Age and Sex

	NC	AD	DLB/AD	DLB/PD
Caudate nucleus	1.73 ± 0.23[a]	1.75 ± 0.35[a]	0.95 ± 0.29[b,c]	0.66 ± 0.27[b,c]
Anterior putamen	2.00 ± 0.27[a]	2.07 ± 0.41[a]	0.80 ± 0.25[b,d]	0.54 ± 0.19[b,d]
Posterior putamen	1.94 ± 0.25[a]	1.94 ± 0.42[a]	0.65 ± 0.23[b,d]	0.45 ± 0.18[b,d]

[a]No significant differences in group means ($p > 0.48$).
[b]Means for DLB/PD and DLB/AD are lower than means for NC and AD groups ($p < 0.001$).
[c]Mean for DLB/PD is marginally lower than mean for DLB/AD ($p = 0.05$).
[d]Means for DLB/PD and DLB/AD are not different ($p > 0.1$).

NC = normal control; AD = Alzheimer's disease; DLB/AD = patients with a diagnosis of dementia with Lewy bodies who developed parkinsonian symptoms simultaneously with or after the onset of dementia; DLB/PD = patients with a diagnosis of dementia with Lewy bodies who developed parkinsonian symptoms at least 1 year before dementia.

Table 3. Mean and Standard Deviation of the Percentage of Asymmetry of the Binding Potential of Striatal Structures after Adjustment for the Covariates of Age and Sex by Weighted ANCOVA

	NC (%)	AD (%)	DLB/AD (%)	DLB/PD (%)
Caudate nucleus	4.4 ± 3.2[a]	6.9 ± 6.0[a]	7.0 ± 5.8[a]	3.6 ± 6.1[a]
Anterior putamen	5.2 ± 2.5[a]	4.4 ± 4.8[a]	7.9 ± 8.9[a]	6.7 ± 3.4[a]
Posterior putamen	6.7 ± 3.7[a,b]	4.8 ± 8.3[a,b]	14.5 ± 18.1[b,c]	16.5 ± 12.6[c]

[a]No significant group difference in group means ($p > 0.1$).
[b]Mean for DLB/AD is higher than means for NC and AD ($p \leq 0.03$).
[c]Means for DLB/PD and DLB/AD are not different ($p > 0.8$).

NC = normal control; AD = Alzheimer's disease; DLB/AD = patients with a diagnosis of dementia with Lewy bodies who developed parkinsonian symptoms simultaneously with or after the onset of dementia; DLB/PD = patients with a diagnosis of dementia with Lewy bodies who developed parkinsonian symptoms at least 1 year before dementia.

tically shows marked asymmetry in both presynaptic terminals[28] and dopaminergic D2 receptors,[29] with the asymmetry correlated to the clinical findings.

We selected cases for study with established diagnoses by currently accepted clinical criteria. The purpose was to determine whether these studies would clearly separate the groups, and, if so, we planned to carry the study into patients with early dementia. The cases selected had equivalent levels of dementia and were well matched in age and duration of disease. The major difference between patient groups was the higher proportion of women in the AD than in the DLB group, reflecting in part the relative prevalence of these disorders in the two sexes. Other factors may have contributed to these differences, but we avoided systematic selection bias by accepting all patients who met diagnostic criteria and agreed to participate. All DLB patients fulfilled criteria for probable DLB according to consensus criteria,[11] and all had clear parkinsonian features.

The finding of decreased striatal monoaminergic terminals in DLB was not surprising, because these patients all had identifiable features of parkinsonism, including bradykinesia, masked face, limb rigidity, and parkinsonian gait. Moreover, as anticipated, we found lower binding levels in the DLB patients whose disorders began with parkinsonian features initially in comparison with those whose disorders began with dementia. One surprising finding was that a few AD patients had binding values below the lower limit of the normal control group, notably in the posterior putamen. We obtained a postmortem examination in one of these cases and found changes typical of both DLB and AD. This patient exhibited no parkinsonian features at the time of study, and mild bradykinesia and rigidity were detected 15 months after the study, 3 months before death. This indicates that the decline in monoaminergic presynaptic terminals occurs well in advance of clinical evidence of parkinsonism and lends some credence to the possibility that in mild cognitive impairment or early dementia we may be able to differentiate

AD from DLB using PET with (+)-[^{11}C]DTBZ. Neuropathology findings on a second patient from the AD group showed no changes typical of DLB and this subject had normal DTBZ binding.

Several published functional brain imaging studies of AD, PD, and DLB cases are relevant to the current investigation. The approaches used have included PET studies of local cerebral metabolic rates for glucose (lCMRglc),[30] single-photon emission computed tomography (SPECT) investigations of local cerebral blood flow,[31] and both PET[32–35] and SPECT[36–39] studies of nigrostriatal projections using ligands that label dopaminergic presynaptic or postsynaptic sites. Three studies examined striatal dopaminergic presynaptic terminals in various groups of cases that included PD, DLB, AD and normal age-appropriate controls using PET with the striatal dopaminergic presynaptic ligand [^{18}F]fluorodopa[32–34] and one with the dopamine presynaptic reuptake ligand [^{11}C]β-CFT.[35] One study using [^{18}F]fluorodopa in a small group of subjects reported results similar to those in the present investigation, that is, decreased uptake in the caudate nucleus and putamen in DLB as compared with AD and normal controls, and no difference between AD and control groups.[32]

The current investigation augments previous studies by showing a marked decrease of striatal binding in DLB, below the range of the normal control group and below the range of most AD patients. Moreover, our findings suggest that AD patients who have striatal binding below the range of the normal controls and in the upper range of the DLB cases may be developing the neuropathological changes of DLB in advance of clinical evidence of parkinsonism. This study shows in DLB patients a modest but significant asymmetry of binding in the posterior putamen but not in the caudate nucleus or anterior putamen. Additional studies will be needed to compare these findings with a group of PD patients with normal cognition to determine whether relative asymmetry of binding might be a useful means of determining whether a disorder that ap-

pears to be PD may later evolve into DLB. Finally, the findings presented here suggest that PET with (+)-[^11^C]DTBZ may be used in patients with mild cognitive impairment or early dementia to differentiate those who will evolve to develop AD from those who will develop AD coupled with DLB. In this context, note that many patients have the combined pathology of AD and DLB.[40,41]

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