Cortical Cholinergic Function Is More Severely Affected in Parkinsonian Dementia Than in Alzheimer Disease

An In Vivo Positron Emission Tomographic Study

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**Background:** Pathology reports have shown that cholinergic forebrain neuronal losses in parkinsonian dementia (PDem) are equal to or greater than those in Alzheimer disease (AD). We hypothesized that patients with PDem would have cholinergic deficits that were similar to or greater than those of patients with AD.

**Objective:** To determine in vivo cortical acetylcholinesterase (AChE) activity in healthy control subjects and in patients with mild AD, PDem, and Parkinson disease without dementia using AChE positron emission tomography.

**Setting:** University and Veterans' Administration medical center.

**Design and Patients:** Group comparison design of patients with AD (n=12), PDem (n=14), and Parkinson disease without dementia (n=11), and controls (n=10) who underwent AChE imaging between July 1, 2000, and January 31, 2003. Patients with AD and PDem had approximately equal dementia severity.

**Main Outcome Measures:** Cerebral AChE activity.

**Results:** Compared with controls, mean cortical AChE activity was lowest in patients with PDem (−20.0%), followed by patients with Parkinson disease without dementia (−12.9%; \( P < .001 \)). Mean cortical AChE activity was relatively preserved in patients with AD (−9.1%), except for regionally selective involvement of the lateral temporal cortex (−15%; \( P < .001 \)).

**Conclusion:** Reduced cortical AChE activity is more characteristic of patients with PDem than of patients with mild AD.

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Since the initial reports of a profound reduction of cortical choline acetyltransferase and cholinergic neuronal loss in patients with Alzheimer disease (AD),1–2 substantial evidence implicates cholinergic hypofunction as a significant component of this disorder. However, recent evidence indicates that cholinergic deficits are not severe in mild AD and become significant only in more advanced stages of this disorder.3–5

The development of positron emission tomographic (PET) technology to measure AChE functional activity offers the prospect of studying cholinergic innervation in vivo at the early stages of neurodegenerative disorders.6 Acetylcholinesterase (AChE) activity in the human AD-affected brain has been mapped using PET and \(^{11}C\)methylpiperidin-4-yl propionate (\(^{11}C\)PMP) and \(^{11}C\)methylpiperidine-4-yl acetate radioligands.7,8 These PET studies reported in vivo reductions of cortical AChE activity that were less than expected on the basis of postmortem data.7,9

Dementia in Parkinson disease (PD) is common, but its precise pathophysiological substrates are not well understood.9–10 Significant loss of cholinergic forebrain neurons has also been reported in PD-affected brains.11,12 Arendt et al13 found greater forebrain neuronal loss in patients with PD than in patients with AD, suggesting that cholinergic deficits may be at least as prominent in (late-stage) PD as in AD. The primary aim of this study was to compare in vivo cerebral AChE activity in patients with mild AD, parkinsonian dementia (PDem), and PD without dementia, and healthy controls (HCs).

**METHODS**

**SUBJECTS**

The study involved 47 subjects (12 with AD, 14 with PDem, 11 with PD, and 10 HCs). There were no significant differences in mean (SD)
age among the groups: those with AD, 74.3 (5.80) years; those with PDem, 72.8 (7.9) years; those with PD, 71.2 (7.9) years; and HCs, 70.0 (8.7) years; F=0.67, P=.51. Mini-Mental State Examination (MMSE) scores (mean [SD]) were decreased in the groups with dementia with those with AD being 22.2 (4.6), those with PDem, 22.8 (5.7), those with PD, 27.3 (2.2), and HCs, 29.4 (0.7); (F=8.30, P<.001) but the scores were not significantly different between the AD-affected and PDem-affected groups (t=0.29, P=.79). The AD- and PDem-affected groups did not differ in mean (SD) scores on the Global Deterioration Scale with those with AD scoring 4.9 (0.7) and those with PDem, 5.0 (0.8) (t=0.27, P=.79).14,15 nor in years of education with those with AD scoring (mean [SD]) 12.8 (2.6) years and those with PDem, 13.5 (3.1) years (t=0.61, P=.60). Sex distribution was different between groups: those with AD, 8 women and 4 men; those with PDem, 1 woman and 13 men; those with PD, 11 men; and HCs, 7 women and 3 men. However, previous AChE PET studies did not find sex differences in cerebral AChE activity.9

The PDem-affected group was evenly divided between patients classified as having idiopathic PD with dementia (n=7) and those having dementia with Lewy bodies (n=7). Idiopathic PD with dementia was diagnosed in patients having a history of idiopathic PD with incident dementia. Dementia with Lewy bodies was clinically diagnosed following the Consortium on Dementia With Lewy Bodies’ criteria.13 Mini-Mental State Examination scores were not significantly different between those who had idiopathic PD with dementia and those who had dementia with Lewy bodies (mean [SD], 23.9 [5.5] and 21.7 [6.1], respectively; t=0.68, P=.46). No subjects were taking anticholinergic drugs. The patients with PDem were taking a variable combination of carbidopa-levodopa, selegeline, and anticholinergic drugs. The patients with PD without dementia (n=7) and those having dementia with Lewy bodies (n=7) were recruited from the Alzheimer Disease Research Center, University of Pittsburgh, Pittsburgh, Pa. Patients with PD or PDem were recruited from the movement disorders clinics at the University of Pittsburgh School of Medicine and the Veterans Administration Healthcare System, Pittsburgh. The results of the neurological examination of the HCs showed no abnormalities. The study was approved by the institutional review boards of the medical centers.

AChE PET AND MAGNETIC RESONANCE IMAGING

The [11C]PMP radioligand is an acetylcholine analogue that serves as a selective substrate for AChE hydrolysis.8 The hydroxylated radioligand becomes trapped as a hydrophilic product locally in the brain following the AChE biodistribution. Acetylcholinesterase has been recognized since 1966 as a reliable marker for brain cholinergic pathways including the human brain.16,17 Acetylcholinesterase is localized predominantly in cholinergic cell bodies and axons. In the cortex, AChE is present in axons innervating it from the basal forebrain.19 There also is AChE in intrinsic cortical neurons and low levels of AChE are probably present in the noncholinergic structures postsynaptic to the nucleus basalis innervation.20 These data support the validity of [11C]PMP PET as a reliable marker of the forebrain cholinergic system. The [11C]PMP was prepared using a previously described method.21 Dynamic PET scanning was performed for 80 min-

Average and regional neocortical AChE activities for the different groups are shown in the Table. Compared with HCs patients with PDem showed the greatest reductions in average frontal, parietal, and temporal neocortical [11C]PMP k3 hydrolysis rates (−20.0%) in the disease groups, followed by patients with PD without dementia (−12.9%; P<.001). Patients with AD had the smallest cortical reductions (−9.1%), with the exception of the lateral temporal neocortex. Temporal subregion analysis revealed greater reductions in the inferior lateral temporal cortex than the superior regions in all groups compared with HCs: those with PDem, −27.2%; those with PD, −22.5%; and those with AD, −17.6% (F=8.29, P<.001; Figure). There were no significant left-right hemispheric differences observed. Right-sided hippocampal AChE activity was significantly reduced only in PDem-affected patients but tended to be lower in the AD-affected group compared with HCs (Table).

DATA ANALYSIS

The frames of the dynamic [11C]PMP PET data set were individually aligned to eliminate interframe registration errors attributable to patient movement using the automated image registration algorithm of Woods et al.22 The cropped MRI was registered to the PET data using a modified version of automated image registration.23 The registered MRI and the Co-Planar Stereotactic Atlas of the Human Brain by Talairach and Tournoux24 were used to identify regions of interest (ROIs). The frontal ROI was drawn on the MRI to include dorsolateral prefrontal association (5 slices), anterior cingulate (7 slices), and orbitofrontal cortices (4-5 slices). The parietal ROI included both superior (4 slices) and inferior posterior (4 slices) lateral parietal association cortices. The lateral temporal ROI included the superior (4 slices) and inferior (3 slices) lateral association cortices. Separate ROIs were drawn over the amygdala (3-4 slices) and hippocampus (3-4 slices). All MRIdrawn ROIs were transferred to the PET data. Average neocortical [11C]PMP k3 (hydrolysis rate) activity was calculated as a composite score from frontal, parietal, and lateral temporal association cortices. A noninvasive kinetic analysis of the k3 hydrolysis rate (AChE activity) was performed using a direct estimate of k3 without use of an arterial input function, based on the shape of the tissue time–activity curve alone.26 The shape analysis method has been compared with the more standard compartmental analysis using arterial input functions and non-linear least squares estimation, and it showed that the noninvasive shape analysis approach gave similar results to kinetic analysis in the brain cortex.27 Analysis of variance with Dun-
Hydrolysis rate; DLB, dementia with Lewy bodies; PD, Parkinson disease without dementia; PDD, idiopathic PD with dementia; PDem, parkinsonian dementia.

et al8 found slightly greater cortical AChE activity reduction in PD.27,28 Therefore, degeneration of the cholinergic system may play a significant role in the cognitive decline in PD. Previous imaging studies have reported cholinergic deficits in patients with PD.29,30 Our study demonstrated that cortical AChE deficits were greatest and more extensive in PDem compared with AD of approximately equal degree of dementia severity. A novel finding was that cortical AChE activity in the patients with PD was intermediate between the PDem- and AD-
affected groups. Our findings agree with postmortem evidence suggesting that a primarily basal forebrain cholinergic system degeneration appears early in PD and then worsens with the onset of dementia.11

Findings of reduced radioligand activity in patients with dementia raise questions about the effect of partial volume effects due to cerebral atrophy. Koepp et al12 have discussed how the shape analysis approach, which inherently is entirely insensitive to the scale of the data, is nearly unaffected by tissue atrophy. In addition, Kuhl et al13 have demonstrated that cortical AChE activity did not change as a result of changes in blood flow and that cerebral atrophy had little influence on the measures of cortical AChE activity. As cortical AChE activity reductions in the patients with PD without dementia were generally greater than in patients with AD, these cholinergic reductions are unlikely to be explained by partial volume effects.8

Although prevailing diagnostic criteria for dementia with Lewy bodies distinguish it from AD and idiopathic PD with dementia, it is unclear whether dementia with Lewy bodies and idiopathic PD with dementia are part of the same disease spectrum or are distinct disorders. Our data show that average neocortical cholinergic denervation does not differ between patients with idiopathic PD with dementia and patients with dementia with Lewy bodies and support the view that idiopathic PD with dementia and dementia with Lewy bodies lie on a common disease spectrum with respect to cholinergic pathophysiology.

In conclusion, these findings support a cholinergic model of dementia that may be more applicable to PDD than prototypical AD.

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