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Gray Matter Atrophy Associated with Extrapyrarnidal Signs in the Lewy Body Variant of Alzheimer's Disease

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Abstract

Up to 60% of the patients with Alzheimer's disease (AD) can have cortical or brainstem Lewy bodies (LB), and extrapyramidal signs (EPS) have been found to be associated with LB in AD patients. However, the relationship between EPS and brain volumes has not been studied in the LB variant of AD using structural magnetic resonance imaging (MRI). The purpose of this study was to determine the relationship between patterns of brain atrophy and clinical EPS in patients with pathologically confirmed AD. We compared gray matter structure using voxel-based morphometry in 29 Definite AD cases, 16 (55%) of whom also had LBs identified with α -synuclein immunohistochemistry. Multivariate models analyzed brain volume at a voxel level accounting for subject group, Mini-Mental State Examination (MMSE), EPS, total brain volume, and the time from MRI scan to death. There was no significant difference in gray matter volume in the Definite AD patients as a function of LB. There was a significant association between gray matter volumes and the MMSE in AD patients, both with and without LBs. There was a significant correlation between gray matter volume and EPS only in the group of AD patients with LBs, and not in those with pure AD. These findings suggest that the etiology of EPS in patients with the LB variant of AD is associated with neuronal loss in the nigrostriatal tracts. By contrast, the source of the EPS in AD alone appears to be less well localized.

Keywords

Alzheimer's disease; extrapyramidal signs; imaging; Lewy bodies; magnetic resonance imaging; voxel-based morphometry

INTRODUCTION

Alzheimer's disease (AD) is a degenerative neurological disorder whose prevalence of increases with age, affecting 10% of individuals over 65 years of age and more than 50% over 85 [1]. AD is characterized by the deposit of amyloid plaques and neurofibrillary tangles [2], and the progression of the pathology of AD is expressed in the protocol of Braak staging [3] with the first changes occurring in the mesial temporal lobe, and spreading in an orderly sequence to other brain areas. In addition, Lewy bodies (LBs) identified with α -synuclein-based methods can be found in the neocortex and brainstem in up to 60% of patients with autopsy confirmed AD [4].

Extrapyramidal signs (EPS) are common in patients with AD [5]; they are more frequent as the disease progresses, and they predict more rapid progression of the disease [6]. Studies conducted in large autopsy-based series have shown that EPS are associated with LBs in AD patients, and these patients developed EPS earlier than those without LBs and had a faster progression to disability [7]. Therefore, the study of the relationship between LBs and AD pathology is important in order to understand the factors associated with disability in AD patients.

The neuropathological substrates of EPS in AD are not clear. AD patients with EPS do not necessarily have LBs in the substantia nigra and locus ceruleus, and it has been suggested that extranigral lesions involving the mesocortical dopaminergic pathways play a role in the development of EPS in AD [8]. Some autopsy studies have found that AD patients with EPS had more neurofibrillary tangles in the substantia nigra than those without EPS [9], raising the possibility that the presence of EPS was secondary to an early nigral dysfunction (e.g., cytoskeletal abnormalities, altered synapses). However, the severity of neuronal loss in the substantia nigra did not explain the presence of EPS. Similarly, patients with the LB variant (LBV) of AD can manifest EPS in the absence of nigral damage, and with LBs distributed solely in neocortical areas [4].

One of the limitations of autopsy studies is that they usually provide a cross-sectional view of late stage disease. Therefore, the use of magnetic resonance imaging (MRI) data acquired early in the course of dementia and linked with autopsy confirmation of the disease can provide critical information for understanding the early pathophysiological changes associated with EPS in AD. We report here the results of the analysis of structural MRI scans obtained from patients when they first enrolled in the University of Pittsburgh Alzheimer's Disease Research Center (ADRC). The patients were selected for study because they all came to autopsy and met the criteria for Definite AD, with or without LBs. We then studied the brain regional volumes measured at study entry at the voxel-level, and correlated volume with measures of cognitive and motor functions. This provided us with the opportunity to compare and contrast the brain structural changes that occur early in AD with and without LBs, and their relationship to the presence of EPS.

METHODS

We examined the relationship between gray matter volume on MR images and clinical symptoms of dementia in 29 autopsy-proven patients with Definite AD. Each patient received an extensive neuropsychiatric evaluation including medical history and physical examination, neurologic history and examination, semi-structured psychiatric interview, and neuropsychological assessment [10, 11]. All patient records were reviewed by the study team at a multidisciplinary clinical consensus conference for assignment of a diagnosis.

Each patient was interviewed by a nurse practitioner or physician's assistant (PA) to identify any physical and cognitive limitations, as well as the burden to their primary caregiver. The

neurologic examination was performed by both a neurologist and a PA trained in the medical examination of the elderly; each abnormal sign detected by the PA was corroborated by the neurologist. The neurologic examination included assessments of buccolingual and limb praxis, motor impersistence, dressing praxis, cranial nerves, motor tone and abnormal movements, deep tendon reflexes, plantar response, primary sensory testing, stereognosis and graphesthesia, cerebellar testing, release signs, gait abnormalities, and peripheral pulses (including carotid auscultation). The neurologists and the PA completed the New York University (NYU) Scale for Parkinsonism, which is a rating tool to track the longitudinal course of signs and symptoms related to Parkinson's disease [12]. It includes indices of 1) cognition, behavior, and mood; 2) activity of daily living; and 3) motor functions, and ratings are made, for example, regarding speech, facial expression, tremor, rigidity, postural stability, walking, etc. Each is rated on a 0–4 point scale, with '4' being most affected.

Each individual set of results was reviewed at a clinical consensus conference (neurologists, neuropsychologists, and psychiatrists), and all of the patients were classified using the clinical research criteria for AD [13] and for dementia with Lewy bodies (DLB) [14]. The diagnosis of DLB was based on the consensus guidelines for the clinical and pathological diagnosis of DLB. Patients were classified as having Probable DLB when they had dementia and two of the three core features (i.e., fluctuating cognition with pronounced variations in attention and alertness, recurrent visual hallucinations, or spontaneous motor features of parkinsonism), and Possible DLB when dementia and only 1 core feature was present (See [10, 15, 16] for details).

Inclusion and exclusion criteria

The clinical criteria for entry into the ADRC registry includes progressive cognitive deficits, age >40, native English speaker, adequate visual and auditory acuity to complete neuropsychological testing, and a reliable caregiver who is capable of providing accurate information about the patient's history and symptoms. The clinical exclusion criteria were a lifetime history of schizophrenia, manic-depressive disorder or schizoaffective disorder, a history of electroconvulsive therapy, current alcohol or drug abuse/dependence, history of alcohol or drug abuse/dependence within 2 years of the onset of the symptoms of dementia, history of cancer within the previous 5 years, and any significant disease or unstable medical condition that could affect neuropsychological testing.

All of the data included in this report came from patients who had been followed longitudinally in the ADRC, who came to autopsy, and who had undergone an MRI scan of the brain at the center at study entry. All of the patients met criteria for Definite AD, and 16 of them also had LBs present identified with α -synuclein immunohistochemistry.

Neuropathologic diagnosis

The neuropathologic diagnosis of AD was based on the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropathologic criteria [17], and the National Institute on Aging and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of AD [18]. All cases met the CERAD criteria for AD, and the National Institute on Aging and the Reagan Institute Working Group criteria of a moderate or high likelihood that the dementia was due to AD pathology. Neurofibrillary tangle staging was done using the system of Braak and Braak [3].

LBs were identified using LB509 (diluted 1 : 200, Zymed, San Francisco, CA), a well characterized monoclonal antibody against α synuclein. The deparaffinized sections of the appropriate brain regions were digested for 1 min with 100 mg type XXIV Protease (Sigma)

in 350mL of distilled water to 3°C followed by primary antibody diluted in common antibody diluent. The staining was visualized using the LSAB-2 Kit (Dako, Carpinteria, CA) with diaminobezidine, and counterstained with Mayer's hematoxylin. All round, α -synuclein-positive structures were considered to be LBs, including intracytoplasmic, intraneuritic, and extracellular LBs. LBs were considered cortical only if they were found in frontal, temporal, or parietal neocortex [4].

Subjects were classified according to the Consensus Guidelines for the Clinical and Pathologic Diagnosis of DLB: scores of 1 to 2 indicated predominant brainstem (with limited transentorhinal and cingulate gyrus) involvement, scores of 3 to 6 indicated predominant limbic and limited neocortical involvement, and scores of 7 to 10 indicated predominant neocortical involvement [19]. These groupings were then simplified both in terms of their Braak stage (Low: III/IV; High: V/VI) [3], and the α -synuclein staining for LBs (None; Subcortical (1–6); Neocortical (7–10)) [14].

MRI scanning and voxel-based morphometry (VBM) analysis

MR images were collected using a 1.5 T Signa scanner (GE Medical Systems). The subjects were positioned in a standard head coil, and a volumetric spoiled gradient recall sequence with parameters optimized for maximal contrast was acquired in the coronal plane (repetition time, 25 ms; echo time, 5 ms; slice thickness, 1.5 mm; 0 mm gap; 40° flip angle, and field of view, 24 × 18 cm).

The scans were reoriented into the axial plane and then normalized to a custom “older brain” template [20], based on 416 healthy elderly subjects. The normalized images were then segmented using a mixed model cluster analysis which assigns each voxel a value reflective of a tissue type based on prior probabilities from the custom template. The segmented images were modulated by multiplying these files by the Jacobian determinant of their spatial transformation matrix, and the resulting images were smoothed using a 10 mm isotropic Gaussian filter. The initial processing of the scans was run as a semi-automated script in SPM2 (<http://dbm.neuro.uni-jena.de/vbm.html>).

Statistical analysis

Group differences were analyzed with χ^2 and *t*-tests (SPSS for Windows, v15). The modulated gray matter images were analyzed in SPM5 using subject group, total brain volume, Mini-Mental State Examination (MMSE) [21], and the New York University Scale for Parkinsonism [12] as subject-specific covariates. Following the identification of the specific areas of regional atrophy, eigenvariates were extracted from within SPM2; spheres of 10 mm radius were centered at the local maxima within the region identified for the comparison of two groups. The regions of significant differences were projected onto a standard young brain (colin27).

RESULTS

There were no statistical differences between AD patients and those with LBV in terms of age at study entry, age at death, gender, the time from initial symptom onset to first clinic visit, the time from MRI scan to death, education level in years, MMSE, Blessed Dementia Rating Scale for Activities of Daily Living [22], Hachinski Ischemic Scale [23], Hamilton Depression Scale [24], or NYU Scale (Table 1). There were no significant differences in the individual items of the NYU Scale (Odds Ratios 0.76–2.50, all *p*'s > 0.05).

Braak staging was not significantly different between the AD patients with and without LBs ($\chi^2 = 0.02$, *df* = 1). Within the LBV group, 10 of the cases had neocortical LBs, and none had only brain-stem LBs. There was no association between the severity of Braak staging

and the presence or location of the LBs ($\chi^2 = 0.235$, $df = 2$). Among the patients with Definite AD alone, none had a clinical diagnosis of either Possible or Probable DLB. Among the individuals with Definite AD *and* LBs, 13/16 had an initial clinical diagnosis of Probable AD, two were classified as mild cognitive impairment, and one with Dementia (Not otherwise specified); one of the AD patients had a secondary diagnosis of Probable DLB. At the time of the final clinical evaluation of the LBV patients, the two with mild cognitive impairment now met criteria for Probable AD, and one of these also had a diagnosis of Possible DLB.

Relationship between brain atrophy and LB

There were no statistical differences between LBV and AD groups in terms of gray and white matter volumes as a percentage of total intracranial volume (TIV) (Table 2) (MANCOVA $F(2,26) = 1.74$, $p = 0.20$). The VBM analysis of the gray matters volumes revealed no areas whose volumes were significantly different between groups even when we used an uncorrected threshold of $p < 0.001$.

Relationship between pathological markers and MRI atrophy

We investigated the relationship between diagnosis and brain atrophy further by testing the association between the pathological markers of the two diseases and MRI-measured volume at the voxel level. The VBM analysis included the Braak Stage (III/IV versus V/VI) and the LB staging (None, Brainstem/Limbic, Neocortical) as covariates with age and TIV. There were no associations between the Braak or the LB staging and gray matter atrophy (False Discovery Rate (FDR) $p < 0.05$) [25].

Relationship between clinical symptoms and MRI atrophy

We evaluated the relationship between the clinical symptoms at the time of the MRI scan and the gray matter integrity. The VBM analysis included MMSE score, NYU score, age, and TIV as covariates. There was no significant difference between groups at the voxel-level, and overall no significant associations between the MMSE score and brain volume (FDR, $p > 0.05$). We also tested the interaction between group (AD versus LBV) and the MMSE and NYU scores on gray matter volumes. There was no significant interaction between Group and MMSE score; that is, the effect of MMSE on gray matter volumes did not differ as a function of group. However, there *was* a significant interaction between Group and NYU score. Specifically, in the LBV patients there was a significant area of positive correlation between NYU scores and volume (see Fig. 1). The volume of the putamen (left > right) was significantly linked to the score on the NYU scale in the LBV patients only (left putamen: 6371 voxels, peak = X: -31, Y: 8, Z: 15; FDR $p = 0.015$, $t = 7.94$). The volume contained in the region of the left putamen did not differ significantly between the groups ($t(26) = 1.28$, $p = 0.23$); in the AD group there was no association between the NYU Scale and brain volumes.

DISCUSSION

Although there have been several neuroimaging studies of AD and DLB (see, for example, [26, 27]), this is one of the first to compare the patterns of cerebral atrophy on MR images in autopsy-confirmed AD patients with LBs relative to those without (cf., [28]). The major finding from this study is that the severity of the EPS at the time of the scan was significantly associated with atrophy in the putamen among the LBV patients, but not the AD patients. This suggests that while the EPS in the LBV patients are likely secondary to losses in the nigrostriatal tracts, the source of the EPS in AD alone is less well localized.

This finding is important because in spite of the host of studies examining the differences in regional brain volumes between patients with AD and those with LBV or DLB, we are not aware of any studies that have examined the relationship between EPS and gray matter atrophy in autopsy confirmed cases. Our finding of a significant interaction between Group and NYU score (but not Group and MMSE score) speaks directly to the underlying pathophysiology of the EPS in LBV and AD. The lack of an interaction between Group and MMSE means that the relationships between brain volumes and global cognition do not differ between the two groups, although we did not examine this interaction in specific cognitive domains.

The high correlation between NYU scores and the volume of the putamen in the LBV patients points toward damage to the nigrostriatal pathways as being critical for the development of the symptomatology. Atrophy in the nigrostriatal tracts progresses in an orderly fashion, and as the LBV patients were relatively early in their clinical course, and the scores on the NYU scale were not high (mean = 18), we would expect more damage to have occurred in the lateral, caudal, and ventral portions of the substantia nigra [29], which should result in alterations in the dorsal and caudal putamen (e.g., [30]). The lack of such an association in the AD patients suggests that the EPS in these subjects may have had a different, or at least a less consistent neuropathological basis, although this may change later in the course of the disease. The fact that the two groups of patients had equivalent atrophy in the basal ganglia further emphasizes the likelihood of differing pathologies being responsible for this gray matter loss.

Our data have implications for understanding the pathophysiology of EPS in the context of AD. First, the fact that there was a significant link between the volume of the putamen and the severity of EPS in the LBV group but not the pure AD group suggests that the LBs were, in fact, causing neurodegeneration, likely secondary to damage to the nigrostriatal tracts. We speculate that if high resolution tractography could be accomplished in the nigrostriatal pathways, we should be able to visualize greater degeneration in the LBV patients relative to the AD patients. Indeed, a recent study using diffusion tensor imaging provided evidence of altered structural integrity in the nigrostriatal pathway (reduced fractional anisotropy and increased radial diffusivity) as a function of increasing age [31]. That particular analysis focused on the dorsal and ventral substantia nigra and red nucleus, but we would predict that a high-resolution analysis in LBV would further reveal differentiation between the ventral and dorsal portions of these nuclei (cf., [32, 33]. Second, when EPS occur late in the course of AD, there is an increase in tau-labeled neurofibrillary tangle burden in the substantia nigra, but not α -synuclein pathology (i.e., LBs) [34]. Taken together with our data, this confirms the idea that the underlying cause of the EPS in these two variants of AD is different. On the one hand (AD alone), neurofibrillary tangles develop in the substantia nigra late in the dementia and result in increased motor signs/symptoms. On the other hand (LBV), LBs occur early in the dementia, result in atrophy in the putamen, with an earlier presentation of EPS. Thus, EPS occurring early in the course of dementia, even in the absence of other signs/symptoms of DLB, should raise the possibility of nigrostriatal atrophy.

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Significant Association Between Putamen Atrophy and NYU Score in LBV but Not AD

Fig. 1. Interaction between group (AD versus LBV) and gray matter volume controlling for the Main Effects of Group, age, MMSE, and total intracranial volume (False Discovery Rate, $p < 0.05$). There is a regionally specific correlation in the putamen for the LBV group that does not appear in the AD group. The scatterplot shows the association between the volume of the VBM-defined cluster in the left putamen and the NYU score for both study group (AD – open circles; LBV – filled circles).

Table 1Demographic and clinical characteristics of the patients at study entry (Mean $\pm$ SD)

Characteristics	Definite AD	LBV	Effect size *
Number of cases	13	16	
Braak staging (low/high)	6/7	7/9	1.10
Lewy bodies (none/subcortical/cortical)	13/0/0	0/6/10	0.94
Age at study entry, y	74.9 $\pm$ 9.0	73.9 $\pm$ 9.0	-0.06
Male/female	4/9	7/9	-0.13
Education level, y	13.2 $\pm$ 3.5	13.1 $\pm$ 3.0	0.03
Age at death, y	82.2 $\pm$ 5.4	79.3 $\pm$ 8.1	-0.21
Time from onset of symptoms to initial visit, y	4.7 $\pm$ 3.4	3.5 $\pm$ 2.6	-0.20
Time from MRI scan to death, y	7.4 $\pm$ 4.9	5.4 $\pm$ 3.1	-0.25
Mini-Mental State Examination	21.1 $\pm$ 6.7	17.6 $\pm$ 4.7	-0.30
Blessed Dementia Rating Scale for ADL	4.8 $\pm$ 3.7	5.2 $\pm$ 3.3	0.05
Hamilton Depression Scale	6.2 $\pm$ 3.5	6.4 $\pm$ 5.2	0.03
Hachinski Ischemic Scale	2.8 $\pm$ 2.3	2.4 $\pm$ 1.2	-0.09
NYU Scale for Parkinsonism	8.9 $\pm$ 9.5	13.6 $\pm$ 12.7	0.21

* Phi for category data, r_{pb} for continuous data.

Table 2The brain volumes of the AD patients with LBs and those without LBs (Mean $\pm$ SD)

	Definite AD	LBV	Effect size *
Gray matter volume	633.8 $\pm$ 47.0	644.4 $\pm$ 89.2	0.07
White matter volume	378.8 $\pm$ 47.9	365.6 $\pm$ 47.7	-0.14
CSF volume	347.1 $\pm$ 80.4	351.4 $\pm$ 62.4	0.03
Total intracranial volume (TIV)	1359.7 $\pm$ 156.3	1361.4 $\pm$ 151.0	0.005
Gray matter (percent of TIV)	46.8 (2.6)	47.3 (3.8)	0.08
White matter (percent of TIV)	27.9	26.8	-0.33

* Point biserial correlation (r_{pb}).