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ORIGINAL ARTICLE

Alpha-Synuclein Lesions in Normal Aging, Parkinson Disease, and Alzheimer Disease: Evidence from the Baltimore Longitudinal Study of Aging (BLSA)

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Abstract

Alpha-synuclein (α-synuclein) lesions are characteristic of idiopathic Parkinson disease (PD) and other α-synucleinopathies. To study the frequency of α-synuclein lesions in normal aging and how frequently they coexist with lesions of Alzheimer disease (AD), we examined the autopsy brains from normal and demented subjects in the Baltimore Longitudinal Study of Aging (BLSA) (n = 117). We found that the overall frequency of α-synuclein lesions was 25%, with 100% in 7 cases of PD, 31.5% in 56 cases with AD lesions, and 8.3% among 36 older control brains. Among brains with AD lesions, the frequency of α-synuclein pathology was higher in those with higher scores for neuritic plaques, but not in those with higher scores for neurofibrillary tangles. Our observations indicate that α-synuclein lesions are uncommon in aged control subjects. Finally, the coexistence of Aβ amyloid and α-synuclein pathology in AD brains suggests that the pathogenic mechanism/s leading to the accumulation of Aβ and α-synuclein may be similar.

Key Words: α-Synucleinopathy, Aging, Alzheimer disease, Lewy body, Lewy neurite, Parkinson disease.

INTRODUCTION

Alpha-synuclein (α-synuclein) lesions are characteristic of a group of aging-associated neurodegenerative disorders known as Lewy body diseases (1), the most common of which is idiopathic Parkinson disease (PD), and of multiple system atrophy (2, 3). PD is a movement disorder characterized morphologically by loss of neurons predominantly in the substantia nigra. Involved neurons contain perikaryal inclusions (Lewy bodies [LB]) and dystrophic neurites (Lewy neurites [LN]) enriched with aggregated α-synuclein (4). α-Synuclein is encoded by a gene on chromosome 4 and expressed in presynaptic terminals throughout the central nervous system (5–8). This protein has been implicated in the pathogenesis of PD (9) based on the presence of missense mutations in the α-synuclein gene in families with autosomal dominant PD (10) and the association of this protein with LB (4, 9, 11). α-Synuclein mutations not only accelerate the onset and evolution of PD but also increase the tendency of the protein to aggregate in vitro (12–15).

In the present study, we address two main questions. First, since Lewy body disease and PD are aging-associated neurodegenerative disorders, how common are α-synuclein lesions in normal aging? Although the answer to this question is critical for the definition of pathologic criteria for PD and other synucleopathies, there are few previous studies of α-synuclein lesions in a normal elderly population (16–20). It has been suggested that α-synuclein lesions are not simply part of the normal aging process, but that they always constitute pathologic entities (21). The second question is how often do α-synuclein lesions coexist with the Aβ amyloid (Aβ) and tau lesions of Alzheimer disease (AD), and what are the possible interactions among these aging-associated neuronal "proteinopathies" (20, 22). Indeed, there is evidence from human and experimental animal studies that α-synuclein and Aβ lesions may be synergistic (23–26).

MATERIALS AND METHODS

Subjects

This study was conducted on subjects from the Baltimore Longitudinal Study of Aging (BLSA). This is a longitudinal study of normal aging conducted by the National Institute on Aging with subjects 65 years of age and older enrolled in a prospective autopsy program. Some of these subjects develop neurodegenerative diseases during the course of the study. Therefore, at enrollment and at subsequent 2-year intervals, all BLSA subjects who eventually came to autopsy were examined according to BLSA protocols (27), complemented by a comprehensive medical history, a standardized neurologic examination that included assessment of extrapyramidal disorders, and a battery of neuropsychologic

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tests (28, 29). This battery included the Blessed Information Memory Concentration (BIMC) (30) and the Mini-Mental State Examination (31). In the year between clinical evaluations, participants were administered the telephone version of the BIMC (T-BIMC) (32). Subjects who showed a decline of 3 or more points in the T-BMIC were invited to an in-person evaluation. In addition, we completed a postmortem Dementia Questionnaire (32–35) for each participant.

We examined 117 consecutive postmortem brains from participants in the BLSA (27) who came to autopsy between 1986 and 2002. The clinical diagnoses of the subjects are presented in Table 1 and neuropathologic diagnoses and demographics in Table 2. Among the 117 subjects, 56 were classified clinically as controls, free of cognitive decline or neurologic abnormality. A total of 34 subjects had clinical diagnosis of AD (36) and 7 carried the clinical diagnosis of PD. Among the PD patients, 6 developed dementia in the late stages of the disease and 1 was cognitively normal. The average time interval between the last clinical evaluation and death was 10.4 months.

To gain a better assessment of the frequency of α-synuclein lesions in additional cases of AD, we also examined the autopsy brains of 20 consecutive cases of AD from the Johns Hopkins University Alzheimer's Disease Research Center (ADRC) (mean age, 80.5 years; 14 females and 6 males; Braak neurofibrillary scores: VI, n = 16; V, n = 2; IV, n = 1; III, n = 1).

Autopsies and Neuropathologic Evaluations

Brains were fixed for 2 weeks in 10% buffered formaldehyde. After macroscopic examination, tissue blocks were dissected from frontal, temporal, parietal, occipital, and cingulate cortices, basal ganglia, amygdala, entorhinal cortex, hippocampus, thalamus, brainstem, and cerebellum. The tissue blocks were embedded in paraffin, cut at 10 μm, and stained with hematoxylin and eosin and the Hirano silver method (37). Silver stains were used for neuropathologic diagnosis of AD according to CERAD guidelines (38) and to determine the Braak neurofibrillary AD scores (39). Sections from medulla, pons, midbrain, hippocampus, entorhinal cortex, amygdala, cingulate cortex, and frontal and temporal neocortex were immunostained for α-synuclein, Aβ, and phosphorylated tau. For immunostaining, tissue sections were deparaffinized, treated with H_2O_2, blocked with 3% normal goat serum in Tris-buffered saline, then placed in an automatic immunostainer (Ventana, Tucson, AZ) for incubation with anti-Aβ (gift from Elan Corp., Dublin, Ireland; dilution 1:400), anti-tau (PHF-1; dilution 1:100, a gift of Dr. P. Davies), or anti-α-synuclein antibody (Synuclein-1 from Transduction Laboratories, Lexington, KY; dilution 1:500) for 32 minutes, followed by secondary antibody for 26 minutes, avidin-HRPO for 8 minutes, and diaminobenzidine chloride-H_2O_2 for 8 minutes, copper 4 minutes, hematoxylin 2 minutes, and bluing reagent for 4 minutes. All sections for Aβ and α-synuclein immunostaining were pretreated with 99% formic acid for 5 minutes. The density of cortical LB and perikaryal α-synuclein-positive granules was examined with a 10× objective in 3 randomly selected 3.14 mm^2 fields and graded on a semiquantitative scale according to Hurtig et al (40). Ratings were assigned as follows: 0 = 0; rare = 1 per field; moderate = 2 to 4 per field; and frequent = > 5 per field. Lewy neurites were assessed semiquantitatively as follows: rare = 1 to 2 neurites per field; moderate = 2 to 10 neurites per field; frequent = >10 neurites per field.

TABLE 1. Clinical Diagnoses in the BLSA Cohort

Diagnosis	No. of Subjects
Control	56
PD	7
AD	34
MCI	2
Non-AD dementia	8
Other	10
Total	117

RESULTS

Examination of the 117 brains from the BLSA cohort confirmed the diagnosis of PD in 7 cases, all of which were in advanced stages of the disease, i.e. stages 5 or 6 in the classification proposed by Braak et al (41, 42). Four of these cases also showed lesions of AD. Among the 56 clinical controls, 36 showed no significant AD pathology and were classified as neuropathologic controls. However, we did find AD lesions in the brains of the remaining 20 clinical controls. In total, we encountered lesions of AD in 56 brains. This number includes the brains of 34 subjects with clinical diagnosis of AD and 2 of MCI (43), and 20 clinical controls. Among these cases with AD lesions, 28 were definite AD, 11 probable AD, and 17 possible AD by the CERAD criteria for pathologic diagnosis of AD (38). In 18 brains, we found other neuropathologic lesions consistent with neuropathologic diagnoses of vascular dementia, dementia of unknown origin, and multiple sclerosis. α-Synuclein lesions were found in all 7 of the PD cases (100%), in 17 brains among 56 cases with AD lesions (31.5%), and in only 3 of 36 control brains (8.3%). Neuropathologic diagnoses are presented in Table 2.

Four types of α-synuclein (+) lesions were identified in different regions of the brain: LB, LN, perikaryal granules, and glial-cytoplasmic inclusions (Fig. 1). In PD cases, we identified α-synuclein (+) lesions as follows: nuclei of the X and XII cranial nerves, nucleus ambiguous, raphe nuclei, and lateral reticular nucleus in the medulla oblongata (100%); locus ceruleus, raphe nuclei, and reticular formation in the pons (100%); substantia nigra pars compacta (100%); amygdala (100%), hippocampus (100%); cingulate gyrus (86%); and midfrontal gyrus (86%).

In addition to LB, LN, and perikaryal granules, we observed scant α-synuclein (+) glial cytoplasmic inclusions in all 7 PD cases (Fig. 1). These inclusions were located predominantly in the white matter of midbrain and medulla but also noted in amygdala, cingulate gyrus, and pons. α-Synuclein (+) glial inclusions were seen occasionally in AD brains but not in controls.

Among the 56 brains with AD lesions, 17 (31.5%) displayed α-synuclein (+) lesions, most frequently in substantia

TABLE 2. Neuropathologic Diagnoses, Demographics, and Overall Frequency of α-Synuclein (+) Lesions in the BLSA

Neuropathologic Diagnosis	No. of Cases	Age (Years)	Sex (Male/Female)	No. of Cases with α-Synuclein (+) Lesions	% of Cases with α-Synuclein (+) Lesions
Control	36	83	30/6	3	8.3
PD	7	87	6/1	7	100
AD, definite	28	88	22/6	11	39
AD, probable	11	91	4/7	2	18
AD, possible	17	88	11/6	4	24
Other	18	86	12/6	2	11
Total	117	87	85/32	29	25

The pathologic diagnosis of PD follows Hughes et al (78). In cases of PD with dementia, we used the consensus criteria of McKeith et al (44). The diagnoses of AD follow CERAD criteria (38). The diagnosis AD possible was given to cognitively normal subjects whose brains showed moderate or frequent neuritic plaques (38). Controls were subjects with normal cognition and CERAD neuritic plaque score 0 or A; in terms of neurofibrillary tangles, their Braak scores were II or less. Other diagnoses include vascular dementia, vascular disease not contributory to dementia, hippocampal sclerosis dementia, dementia of unknown origin, and multiple sclerosis (not demented).

nigra, amygdala, and medulla (Tables 2 and 3). In the cerebral cortex, some AD brains showed LB and LN in cingulate and middle frontal gyri (Table 3). The frequency of α-synuclein lesions was 46% in brains with frequent neuritic plaques (CERAD score C) (38), but it was only 17% in brains with moderate or sparse neuritic plaques (CERAD scores B or A, respectively). However, the frequency of α-synuclein (+) lesions was similar in brains with Braak neurofibrillary scores I–II (2 of 9, 22%), III–IV (7 of 27, 25%), and V–VI (3 of 13, 23%). When we examined the frequency of α-synuclein lesions according to neuropathologic diagnoses by CERAD (38), we found lesions in 39% of definite AD, 18% in probable AD, and 24% in possible AD cases (Table 2).

The distribution and frequency of LB and LN in various brain regions are presented in Table 3. As expected, cases of idiopathic PD showed the highest frequency of LB and LN in all regions examined. Control brains showed the lowest frequency of lesions, and the brains of AD cases showed a

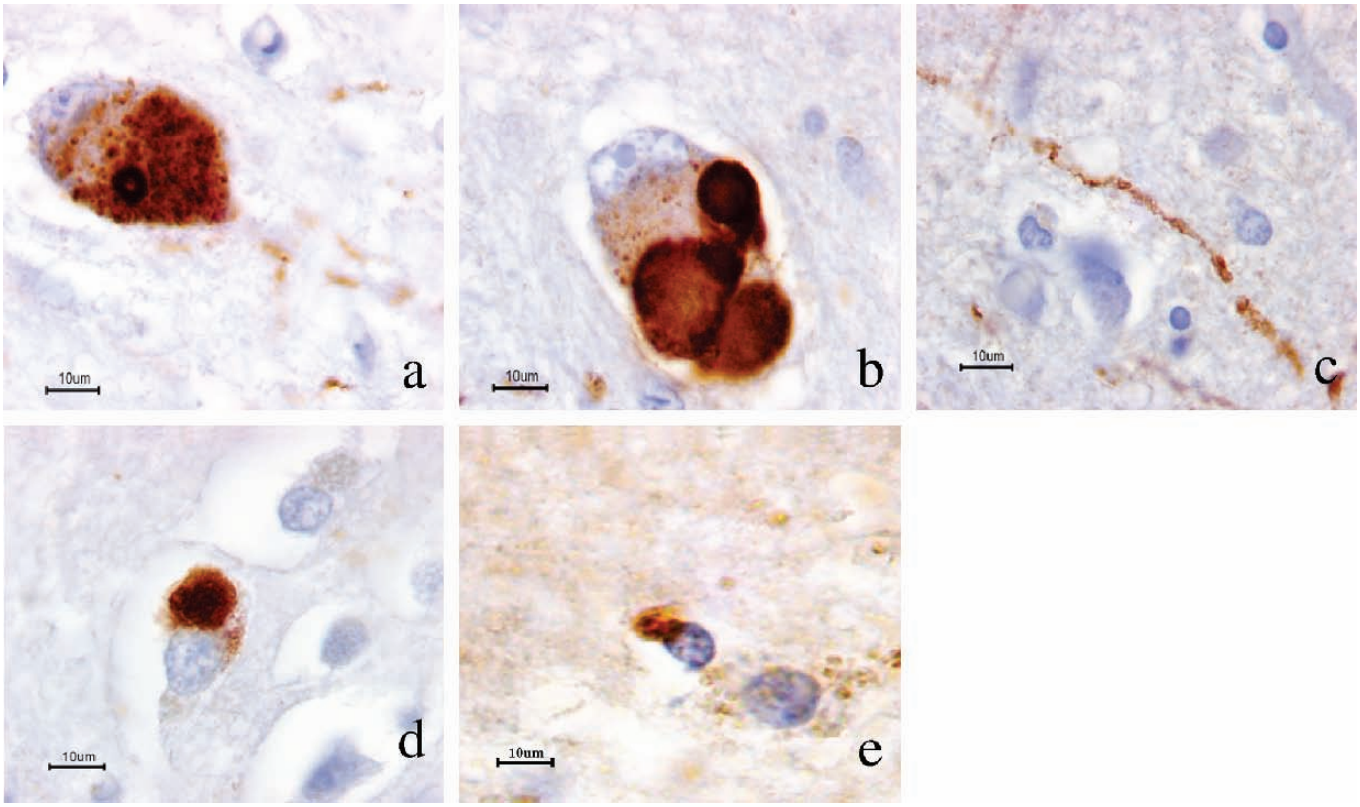

FIGURE 1. α-Synuclein immunostains. Perikaryal granules **(a)**, multiple Lewy bodies **(b)**, and Lewy neurite **(c)** in the substantia nigra of control subjects. Lewy body in the cingulate cortex of an AD case **(d)**. Glial inclusion in the cingulate gyrus white matter of a PD case **(e)**.

TABLE 3. Frequency and Regional Distribution of α-Synuclein Lesions in AD, PD, and Control Group in the BLSA Cohort

Diagnosis	MFG	Cingulate Gyrus	Amygdala	Hippocampus	ERC	SN	Pons	Medulla
PD	6/7 (86)	6/7 (86)	4/4 (100)	4/4 (100)	4/7 (57)	7/7 (100)	6/6 (100)	7/7 (100)
AD definite	3/24 (13)	6/26 (23)	8/17 (47)	7/13 (54)	5/15 (33)	8/19 (42)	4/18 (15)	6/19 (32)
AD probable	2/11 (18)	2/10 (20)	0/3 (0)	1/3 (25)	1/4 (25)	0/76 (0)	0/11 (10)	2/10 (20)
AD possible	0/11 (0)	3/15 (20)	0/4 (0)	0/3 (0)	0/6 (0)	1/11 (9)	1/13 (6)	3/14 (21)
Controls	0/28	1/33 (3)	2/25 (8)	1/13 (8)	1/13 (8)	3/33 (9)	2/29 (7)	2/27 (7)

Values are number of cases α-synuclein (+)/number of cases stained for α-synuclein (percentage of cases with α-synuclein (+) lesions). MFG, middle frontal gyrus; ERC, entorhinal cortex; SN, substantia nigra pars compacta.

Note: α-Synuclein lesions include LB, LN, and perikaryal granules. All sections were not available in each case. The discrepancy between region-specific frequencies of α-synuclein lesions presented here and the overall frequency presented in Table 2 is explained by the unavailability of some tissue sections in some brains.

frequency intermediate between controls and PD. In control brains, α-synuclein lesions were most prominent in substantia nigra pars compacta and medulla oblongata. As shown in Figure 1, these lesions included LB, LN, and perikaryal granules.

In terms of the density of lesions, in cases of PD the highest density of LB and LN was seen in the substantia nigra pars compacta, followed by the cingulate gyrus and medulla; and the density of perikaryal granules had the same distribution. In all categories of AD, the highest density of LB, perikaryal granules, and LN was seen in the amygdala followed by substantia nigra and medulla. In cases of definite AD, the density of LB, perikaryal granules, and LN was frequent, whereas in the corresponding brain regions of probable and possible AD it was moderate.

To confirm the association of AD lesions and α-synuclein pathology, we examined the amygdalae of 20 consecutive cases of AD from the Johns Hopkins University ADRC. α-Synuclein (+) lesions (including LB, perikaryal granules, and LN) were present in 9 cases; this corresponds to 45% of the subjects. In terms of the distribution of α-synuclein lesions within the amygdala, we observed a predominance of lesions in the medial nuclear complex, including the medial, anterior cortical, posterior cortical, and basomedial amygdaloid nuclei. In rare cases, the whole amygdala was involved.

We also compared the clinical features among BLSA subjects who had neuropathologically confirmed diagnoses of AD, with (n = 14) and without (n = 20) α-synuclein lesions. As shown in Table 4, we did not find significant differences in age of onset of dementia, age of diagnosis, age of death, Mini-Mental State Examination at diagnosis, BIMC score at diagnosis, or evidence of parkinsonism.

DISCUSSION

Our results indicate that in the entire BLSA autopsy cohort, 29 of 117 (25%) brains reveal α-synuclein lesions. However, the frequency of these lesions varied greatly across neuropathologic diagnostic categories (Table 2). As expected, all 7 cases (100%) with neuropathologic diagnoses of idiopathic PD showed α-synuclein lesions (Table 2). By contrast, among controls, only 8.3% showed lesions, predominantly involving the brainstem (Table 2). In cases of neuropathologically confirmed definite AD, the frequency of α-synuclein lesions reached 47% in amygdala, 42% in substantia nigra, 54% in hippocampus, and 33% in entorhinal cortex (Table 3). The frequency of α-synuclein lesions was comparable in the amygdala (45%) of AD cases from the ADRC cohort.

Six of the 7 cases of PD were demented. Among them, 4 had coexisting lesions of AD that may have contributed to the cognitive impairment. In the other cases, there was no coexisting neuropathology. Since these subjects developed dementia in the late stages of the disease, they were diagnosed as PD with dementia according to consensus guidelines (44).

Incidence of LB and LN in Normal Aging

The presence of LB and LN in the brainstem of older individuals without clinical histories of PD is well documented in samples of convenience and in cross-sectional studies (45–49). However, there are few studies of α-synuclein lesions in normal aging (16–20, 50). A single study used α-synuclein immunostains to determine the frequency of LB in a longitudinal cohort of aging (16); it described a 12% frequency of LB in nondemented older subjects, a rate close to our observation of 8.3%. Because older studies were based on hematoxylin and eosin stains or ubiquitin immunostains, the presence of dystrophic neurites or LN could not be assessed. With the introduction of α-synuclein immunostains, we and others (45–49) have documented that the brains of few older controls

TABLE 4. Clinical Features of BLSA Subjects With Clinical Diagnosis of AD With and Without α-Synuclein (+) Lesions

[Mean ± SD (Range)]	AD Subjects with α-Synuclein Lesions (n = 14)	AD Subjects Without α-Synuclein Lesions (n = 20)	p Value
Age at onset	83.9 ± 7.1 (65–93)	83.2 ± 5.7 (72–92)	0.84
Age at diagnosis	86.0 ± 6.0 (73–95)	87.1 ± 5.5 (75–96)	0.69
Age at death	89.2 ± 5.0 (83–98)	90.1 ± 5.2 (79–98)	0.65
MMSE at diagnosis	20.5 ± 6.9 (6–27)	21.8 ± 7.5 (11–28)	0.39
BMIC at diagnosis	9.9 ± 4.7 (4–22)	10.5 ± 7.0 (1–26)	0.76
Evidence of parkinsonism	2	7	0.19

MMSE, Mini-Mental State Examination (24); BMIC, Blessed Information Memory Concentration (23).

show both incidental LB and LN. Our observations are also consistent with those of Forno (45) who reported that in controls, LB are frequently localized in the SN and dorsal motor nucleus of the vagus in the medulla. Our observations indicate that α-synuclein lesions do occur in the brains of older neurologically normal control individuals, but these lesions are uncommon, i.e. cranial nerve nuclei of the medulla (7.4%), cranial nerve nuclei of the pons (6.9%), substantia nigra (9%), amygdala (8.3%), and cingulate cortex (3%). The question of whether LBs and LNs in these clinically normal subjects constitute normal aging or the early stages of PD remains unsettled. In a recent report, Del Tredici et al indicated that the earliest lesions of PD occur in the medulla, in the form of α-synuclein lesions of the dorsal glossopharyngeus-vagus coplex (21). Furthermore, Braak et al have proposed that idiopathic PD has a preclinical stage, during which α-synuclein inclusions are present in the brains of individuals free of motor abnormalities (42, 51). If we accept this notion as correct, then 3 controls in our study would be in the preclinical stages of PD, since they all revealed LB and LN lesions in the medulla in addition to the substantia nigra (42, 51). Furthermore, in the control case with the most severe α-synuclein lesions, we reviewed the clinical information and found that this individual had subtle extrapyramidal signs. We concur with the notion proposed by other investigators that incidental α-synuclein lesions in regions known to develop dense LN and LB in PD may represent the preclinical stages of the disease (42, 45, 46, 51, 52). This notion is reinforced by the observation of α-synuclein aggregates not only in cell bodies but also extending into the neurites of affected neurons, which suggests a widespread cellular derangement involving protein processing and intracellular transport (53). Another argument in favor of incidental LB and LN being pathologic is their very low incidence among control subjects (8%–12%). Nonetheless, we cannot be certain that these α-synuclein lesions will necessarily progress to PD in any or all of these individuals.

The α-synuclein-immunostained perikaryal granules present in neurons of the substantia nigra and medulla are within the spectrum of α-synuclein and phosphorylated α-synuclein lesions previously described by Kuusisto et al (50) and Saito et al (17), respectively. We interpret these lesions as another evidence of abnormal processing of α-synuclein, and it is possible they may represent the precursors of LB (17, 50). However, proof of this notion would require a longitudinal study of α-synuclein lesions in animal and/or cell models beyond the scope of the present study.

α-Synuclein lesions were not confined only to neurons but also present as glial cytoplasmic inclusions in all cases of PD, but none in controls. This type of inclusions has been described in normal brain tissue lightly fixed and cut with a vibratome, but not in paraffin-embedded tissues (54). Since our study used paraffin-embedded tissues, we think that in our cases the α-synuclein (+) glial cytoplasmic inclusions are of a pathologic nature. The distribution of glial cytoplasmic inclusions was parallel to that of neuronal α-synuclein lesions, thus, most abundant in substantia nigra, cingulate gyrus, and amygdala. Although glial cytoplasmic inclusions are the characteristic pathologic feature of multiple system atrophy (2, 3), they have also been reported in oligodendrocytes and astrocytes of Lewy body disease and PD (55–61). Since we did not find glial cytoplasmic inclusions in the brains of the few controls who did harbor neuronal inclusions, the involvement of glial cells may likely reflect a more advanced stage of the α-synuclein pathologic process.

α-Synuclein Lesions and AD

The coexistence and interaction of PD with AD have been examined in the past by several studies (23–25, 62), and there is still debate and confusion about diagnostic categories and terminology. Our findings may help to clarify this issue. According to our observations, the severity of AD lesions is a factor influencing the frequency of concurrent α-synuclein lesions. Whereas α-synuclein changes were more frequent in those brains with more abundant neuritic plaques, we did not find a similar correlation with the severity of neurofibrillary tangles as measured by Braak neurofibrillary scores (39), an observation similar to that of previous studies (24, 62). It should be underscored that the frequency of LB in cases of dementia is highly dependent on case selection (16) and immunostaining technique. The frequency of α-synuclein lesions we observed in cases of AD is within the range of most previous studies (63–69). Our results are also similar to two investigations of α-synuclein lesions in demented subjects in 2 other longitudinal studies of aging. Parkkinen et al (16), who also used formic acid enhancement, found lesions in 27% of 103 demented patients, 82% of which had neuropathologic diagnosis of AD. McKee et al (70) examined the brains of 15 subjects from the Framingham Study with neuropathologic diagnosis of AD and reported α-synuclein lesions in the amygdalae in 33% of the cases. However, our observations are different from those reported by Hamilton, who examined 145 cases of sporadic AD cases for the presence of LBs using α-synuclein immunocytochemistry with protease XXIV pretreatment. He reported LBs in 88 of 145 (60.7%) of sporadic AD cases, with the amygdala being the most affected region (62). The difference in the frequency of α-synuclein lesions in cases of AD may be explained by a difference in the sensitivity of the immunostaining and/or a difference in the selection of AD cases. In this regard, a recent report by Hladik and White (71) indicates that pretreatment with proteinase K or protease XXIV is superior to formic acid for demonstrating α-synuclein lesions. To further investigate the question of α-synuclein lesions in AD, we examined the amygdala of 20 cases of AD from the Johns Hopkins University ADRC. The frequency of α-synuclein lesions in these brains was 45%. Because clinical factors may also influence the frequency of concurrent α-synuclein lesions in AD, we compared clinically BLSA subjects with AD dementia (those with neuropathologic diagnoses of definite or probable AD) with and without α-synuclein lesions. As shown in Table 4, we did not find significant differences between these two groups.

The association of higher frequency of α-synuclein changes with neuritic plaques suggests a synergistic effect between the pathogenic mechanisms of AD and PD. This concept has been proposed by several previous studies. Brown et al reported that cortical LBs are significantly more frequent in cases of AD with LB in the substantia nigra than in cases of pure AD or pure PD (23). Mattila et al showed that PD cases

with the apoEe4 allele had a significantly greater number of cortical LBs than those without the apoE 4 allele, an observation that suggests that the pathogenesis of AD is synergistic with that of PD (24). Albeit the mechanism of the synergy between Aβ and α-synuclein pathology is beyond the scope of the present study, it is important to recognize that Aβ is neither necessary nor sufficient for α-synuclein aggregation and the development of LB and LN. These lesions are most abundant in the brainstem, a location where Aβ deposits are absent or rare. Moreover, although the frequency of α-synuclein lesions in AD has been reported to be as high as 60% (62), there is still a 40% of AD cases free of LB or LN. It has been shown that increased levels of Aβ peptides in the brain can promote the formation of intracellular α-synuclein (and also tau) aggregates, but the mechanism for this process remains unclear (72). There is also evidence that Aβ and α-synuclein interact in vitro (73, 74). In addition to direct protein interactions between Aβ and α-synuclein, indirect mechanisms should also be considered. For example, the oxidative stress generated by Aβ may induce or enhance α-synuclein aggregation (75), or Aβ may have toxic effects on proteosomes (9, 76).

Results from our study are consistent with the tenet that there is a synergistic effect of AD and PD and lead us to believe that the LB variant of AD (65, 77) represents the coexistence of PD and AD, with enhancement of cortical α-synuclein lesions by cortical Aβ. Investigations in experimental animals also support the notion that Aβ deposits promote α-synuclein lesions. Masliah et al showed that intraneuronal α-synuclein lesions were more prominent in double transgenic mice carrying the α-synuclein and APP mutations than in α-synuclein single transgenic mice (26).

In conclusion, our observations indicate that α-synuclein lesions, such as LB and LN, are uncommon in older control subjects. However, when these lesions are present in controls, most commonly in the SN and medulla, they may represent preclinical PD. Finally, our observations of frequent α-synuclein lesions in AD are consistent with either of two models: 1) Aβ deposition may cause or enhance α-synuclein lesions, or 2) both lesions are caused by a similar mechanism.

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