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Aβ deposition is associated with enhanced cortical α-synuclein lesions in Lewy body diseases

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Abstract

In order to understand better the neuropathological substrate of dementia in Parkinson's disease (PD) and to examine its interactions with Alzheimer's disease (AD), we examined autopsy brains from 21 cases of PD and Lewy body disease (LBD) with dementia. We separated brains in two groups according to the presence of Aβ deposits. In brains without Aβ, we found few or no Lewy bodies (LB) in the cerebral cortex. By contrast, in brains with Aβ, we observed significant increases in LB in the cerebral cortex ($p < 0.01$) and α-synuclein immunoreactive lesions in the cingulate cortex ($p < 0.01$). Immunoblots of α-synuclein from cingulate cortex in brains with Aβ showed significantly higher levels of insoluble α-synuclein compared to brains without Aβ.

Our observations indicate that in cases of PD with dementia, the neocortex is not necessarily involved by LB. Furthermore, the presence of Aβ deposits in the cerebral cortex was associated with extensive α-synuclein lesions and higher levels of insoluble α-synuclein. This suggests that Aβ enhances the development of cortical α-synuclein lesions in cases of PD.

Keywords: Lewy body disease; Dementia; LBD; Lewy neurites; Parkinson's disease; Aβ; PD; Alzheimer's

1. Introduction

Lewy body diseases (LBD) encompass three main clinicopathological syndromes associated with α-synuclein lesions: Parkinson's disease (PD); dementia with Lewy bodies (DLB), and primary autonomic failure [37]. PD is clinically characterized by bradykinesia, resting tremor, rigidity, gait abnormalities, and postural instability [40]. Although the initial clinical manifestations of PD are predominantly motor, patients frequently develop cognitive decline and dementia as the disease progresses. When motor impairment precedes cognitive decline a year or longer, these patients are classified as PD with dementia [36]. Indeed, since the introduction of therapy with L-DOPA in the 1960s [9], patients with PD survive for many years after the onset of motor manifestations and the frequency of dementia may reach as high as 80% among those with eight or more years of disease duration [1,29,32]. Pathologically, PD is characterized by the degeneration of dopaminergic neurons of the substantia nigra and other subcortical structures, and the presence of α-synuclein enriched Lewy bodies (LB) and Lewy neurites (LN) [6,12,14,17].

DLB is characterized primarily by fluctuating cognitive impairment, attentional deficits, visual hallucinations, and extrapyramidal manifestations. Pathologically, DLB is characterized by LB and LN of variable severity throughout the cerebral cortex, limbic structures, and brain stem [36,37].

LB are spherical, intracytoplasmic, eosinophilic inclusions that contain intermediate filament proteins, ubiquitin, and α-synuclein [46]. The presence of mutations of the α-synuclein gene in kindreds with familial PD supports a role for this protein in the pathogenesis of PD [42].

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The pathologic process leading to the aggregation and accumulation of α-synuclein in neurons and neurites is not known, but one appealing hypothesis is that abnormal post-translational modifications of α-synuclein, such as oxidative damage [15,39,41,43], phosphorylation [26], and/or truncation [31] promote the formation of insoluble aggregates. The degeneration of the substantia nigra and its projection to the striatum is accepted as the substrate of the motor abnormalities in PD, but there is no similar consensus regarding the morphological substrate of dementia in this disorder. Although lesions in various brain regions have been associated with the dementia of PD, in particular LB and LN of the CA2–3 region of the hippocampus [11] and cortical LB [30,44], the precise pathological substrate of dementia in these patients remains elusive [2,4,23,24]. The identification of the lesions responsible for dementia in PD has been hindered by biological and technical factors. PD frequently coexists with Alzheimer's disease (AD) [7,25,34,35], the most common cause of dementia in older subjects, and until recently it has been difficult to discern histologically between the lesions of these two common disorders. Before the advent of α-synuclein antibodies in 1997 [46] immunostaining for ubiquitin was the method of choice to detect LB and LN; however, since the lesions of AD (i.e., senile plaques, neurofibrillary tangles, and dystrophic neurites) are also ubiquitin(+) it was very difficult to separate the histological lesions of the two disorders. In the present study, we use immunostains of α-synuclein, Aβ and tau, specific markers for the lesions and abnormal proteins of PD and AD, and biochemical analyses of α-synuclein to search for the substrate of dementia in PD and to examine the interactions between the two disorders.

2. Materials and methods

2.1. Subjects

We examined brain tissues from all cases of LBD with dementia ($n = 21$) autopsied at the Johns Hopkins Hospital between 1991 and 2002. Under this diagnosis, we include 18 cases of PD and three cases of LBD with dementia. These cases were from the JHU Parkinson's Disease Research Center, the Alzheimer's Disease Research Center, and from the Department of Neurology. The cases included 18 males and 3 females, with an age range between 64 and 90 years and an average age of 77 years. The duration of the Parkinsonian syndrome varied between 1 and 20 years, with an average of 11 years. The duration of the dementia varied between 1 and 14 years, with an average of 8 years. In 18 cases, the motor abnormalities preceded the dementia and we are classifying them as PD with dementia (PDD) [36]. In three cases, the cognitive impairment antedated the motor syndrome. Available

Table 1
Demographic, clinical and neuropathological data

Subject no.	Age	Sex	Duration (years)	CERAD plaque score	Braak NFT score
LBD					
01	75	M	17	O	IV
02[a]	87	M	3	A[b]	II
03	68	M	23	0	II
04	68	M	5	0	II
05	87	M	14	0	II
06	69	M	8	0	III
07	76	M	10	0	II
08[a]	71	M	6	0	II
09	77	M	16	0	II
Mean age 75.3 years[c]					
LBD + Aβ					
10	79	M	14	B	I
11	81	M	?	B	II
12	73	F	7	C	IV
13[a]	90	M	3	B	IV
14	82	M	6	A	IV
15	64	M	8	C	IV
16	82	F	13	B	III
17	84	F	?	A	V
18	77	M	20	B	II
19	84	M	12	C	IV
20	80	M	11	B	IV
21	65	M	19	B	I
Mean age 78.4 years[c]					

CERAD neuritic plaque scores [38] and Braak neurofibrillary scores [5] of LBD cases with (LBD + Aβ) and without (LBD) Aβ deposits.
[a] Indicates cases in which dementia preceded development of Parkinsonism.
[b] Case #02 had a single focus of neuritic plaques, but the remainder of the neocortex was free of Aβ.
[c] The ages of the two groups are not significantly different.