



Philadelphia VA PADRECC

*Parkinson's Disease Research,
Education & Clinical Center*



Dementia in PD is due to diffuse Lewy body disease: No

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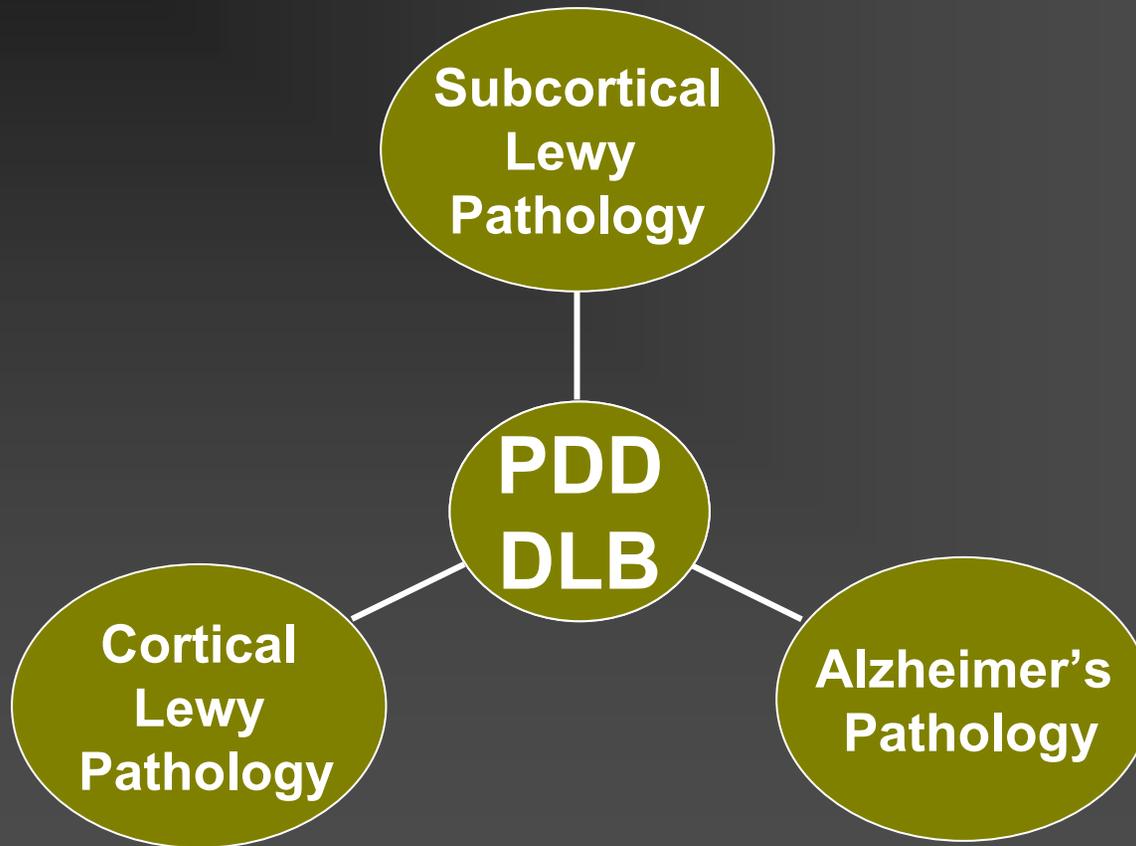
**National VA Parkinson's Disease
CONSORTIUM**
Education • Collaboration • Advocacy





"I'm stumped.
We'll have to wait for
the autopsy."

Why do some patients with PD get demented?



Clinicopathologic Studies of Dementia in PDD prior to α -Synuclein

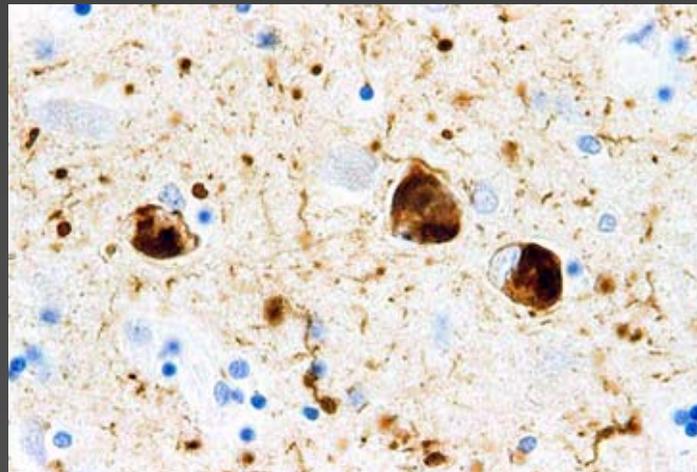
	# of Patients	Proposed Cause
Hakim & Mathieson 1979	19	AD pathology
Boller et al. 1980	16	AD pathology
Mann & Yates 1983	3	Noradrenergic and Cholinergic Degeneration
Whitehouse et al. 1983	5	NBM degeneration
Gaspar & Gray 1984	18	AD, NBM, Locus ceruleus
Perry et al. 1985	10	NBM
Chiu et al. 1986	4	NBM, LC, SN
Jellinger 1987	104	AD, NBM, LC, DLBD
Yoshimura 1988	37	NBM, LC, AD
Rinne et al. 1989	11	Medial Nigra degeneration
Braak & Braak 1990	10	Entorhinal tangles
Xuereb et al. 1990	17	Subcortical disease

Clinicopathologic Studies of Dementia in PDD prior to α -Synuclein

	# of Patients	Proposed Cause
Zweig et al. 1993	7	Subcortical degeneration
Duyckaerts et al. 1993	10	AD
Hughes et al. 1993	31	None in majority, AD
Sugiyama et al. 1994	4	Cortical LB disease
de Vos et al. 1995	12	AD
Jendroska et al. 1996	23	Cortical LB and AD
Jellinger 1997	153	AD
Brown et al. 1998	6	Cortical LBs
Mattilla et al. 1998	41	Cortical LBs
SantaCruz et al. 1999	8	AD

Clinicopathologic Studies of Dementia Late in PDD after α -Synuclein

	# of Patients	Proposed Cause
Hurtig et al. 2000	42	Cortical LB disease
Matilla et al. 2000	45	Cortical LB disease
Apaydin et al. 2002	20	Cortical LB disease
Kovari et al. 2003	22	Cortical LB disease
Aarsland et al. 2005	22	Cortical LB disease



High Density β -Amyloid Plaque Pathology



So why do some patients with PD get demented early?

- Most studies agree that Lewy pathology does not differentiate early from late onset dementia
- However, several studies suggest that early onset patients have more senile plaque pathology and possibly more tangle pathology than late onset

	n	Proposed Cause
Harding et al. 2001	65	Cortical LBs & amyloid plaques
Galvin et al. 2006	103	38% DLB, 32% IPD/AD, 24% IPD
Ballard et al. 2006	57	Cortical LBs & amyloid plaques
Jellinger et al. 2007	330	35% IPD/AD, 22% DLB



Differences in neuropathologic characteristics across the Lewy body dementia spectrum

C. Ballard, MRCPsych; I. Ziabreva, PhD; R. Perry, FRCPath; J.P. Larsen, MD; J. O'Brien, FRCPsych; I. McKeith, FRCPsych; E. Perry, DSc; and D. Aarsland, MD

- 57 patients w/ parkinsonism & dementia
 - DLB 29
 - PD+D < 9 yrs 14 Group A
 - PD+D > 9 yrs 14 Group B
- Longer duration of parkinsonism before dementia correlated with less severe amyloid plaque and α -synuclein scores
- Braak tangle scores are no different
- “The findings do not support an arbitrary cut-off between the two disorders”

University of Pennsylvania Cohort Demographics

Variable		Mean \pm Std. Dev.
Sex	Male	38 (76%)
	Female	12 (24%)
Age of disease onset		63.92 \pm 10.66
Age of dementia onset		73.65 \pm 7.78
Time to dementia		9.85 \pm 6.41
Age at death		77.92 \pm 7.39
Disease duration		14.06 \pm 7.88
Dementia duration		4.28 \pm 2.89

Pathology

CERAD	0	18 (36%)
	A	7 (14%)
	B	13 (26%)
	C	12 (24%)
LB Stage	Transitional	13 (26%)
	Diffuse	37 (74%)
Braak Stage	I-II	20 (40%)
	III-IV	22 (44%)
	V-VI	8 (16%)
DLB Probability	Low	1 (2%)
	Intermediate	13 (26%)
	High	36 (72%)

Pathology Associations

	LB Stage	Braak Stage	CERAD
DLB Probability	.341 (.015)	-.684 (.000)	-.172 (.232)
LB Stage		.113 (.433)	.372 (.008)
Braak Stage			.535 (.000)

Spearman's rho (sig.)

Relationship between Lewy Pathology Distribution and Disease Characteristics

	LB Stage		
	Transitional	Diffuse	Sig.
Age disease onset	65.33 ± 12.02	63.44 ± 10.31	.353
Age dementia onset	76.09 ± 6.76	72.89 ± 8.01	.241
Time to dementia onset	11.64 ± 9.04	9.29 ± 5.39	.757
Age at death	80.33 ± 6.24	77.14 ± 7.63	.208
Disease duration	15.00 ± 8.82	13.75 ± 7.64	.849
Dementia duration	4.27 ± 1.42	4.29 ± 3.24	.332

Relationship between Probability of DLB Phenotype and Disease Characteristics

	DLB Probability		Sig.
	High	Intermediate	
Age disease onset	62.92 ± 10.66	66.36 ± 11.79	.146
Age dementia onset	73.00 ± 7.74	75.31 ± 7.96	.256
Time to dementia onset	9.94 ± 6.12	9.62 ± 7.37	.797
Age at death	77.03 ± 7.45	80.14 ± 6.98	.187
Disease duration	14.18 ± 7.43	13.79 ± 9.17	.593
Dementia duration	4.06 ± 2.88	4.85 ± 2.97	.399

Relationship between Neurofibrillary Tangle Distribution and Disease Characteristics

	Braak Stage		
	I-II	III-IV	V-VI
Age disease onset	59.11 ± 9.63	66.77 ± 10.62	66.88 ± 10.16
Age dementia onset	71.47 ± 8.70	74.67 ± 6.77	75.63 ± 8.14
Time to dementia onset	12.29 ± 6.38	8.29 ± 6.08	8.75 ± 6.49
Age at death	75.63 ± 8.56	78.86 ± 5.93	80.75 ± 7.36
Disease duration	16.56 ± 6.78	12.09 ± 7.78	13.88 ± 9.76
Dementia duration	4.06 ± 2.33	4.14 ± 3.04	5.13 ± 3.76

Highlighted text indicates sole statistically significant difference between groups (sig. = .042)

Relationship between Plaque Density and Disease Characteristics

	CERAD		Sig.
	Low (0, A)	High (B,C)	
Age disease onset	59.75 ± 11.36	68.08 ± 8.19	.016
Age dementia onset	71.23 ± 8.55	75.88 ± 6.41	.076
Time to dementia onset	12.09 ± 7.00	7.79 ± 5.14	.030
Age at death	76.29 ± 8.41	79.48 ± 6.01	.218
Disease duration	16.54 ± 8.32	11.58 ± 6.68	.027
Dementia duration	4.82 ± 3.02	3.79 ± 2.75	.074

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