



Age-Related Neurodegenerative Diseases Represent Common Causes of Rapidly Progressive Dementia

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INTRODUCTION

A clear understanding of the common causes of rapidly progressive dementia (RPD) is needed to prioritize diagnostic testing, enhance diagnostic accuracy, and improve clinical management. Yet most series evaluating the causes of RPD rely on clinical diagnoses without pathological confirmation. This approach may underestimate the contributions of Alzheimer disease (AD) and AD-related dementias (AD/ADRD) to RPD. Additionally, heterogeneity in clinical presentation and the potential for multiple distinct neuropathologies to manifest in individual patients emphasizes the need for comprehensive neuropathological data to inform the pathological contributors to RPD.

We previously reported that rapidly progressive presentations of AD/ADRD accounted for 3.6% of cases accrued within a large neurodegenerative brain bank from 1998 to 2020. Here, we update experience, including cases accrued over the past 5 years.

OBJECTIVES

Determine the neuropathological causes of RPD in cases accrued over 25 years within a neurodegenerative brain bank.

METHODS



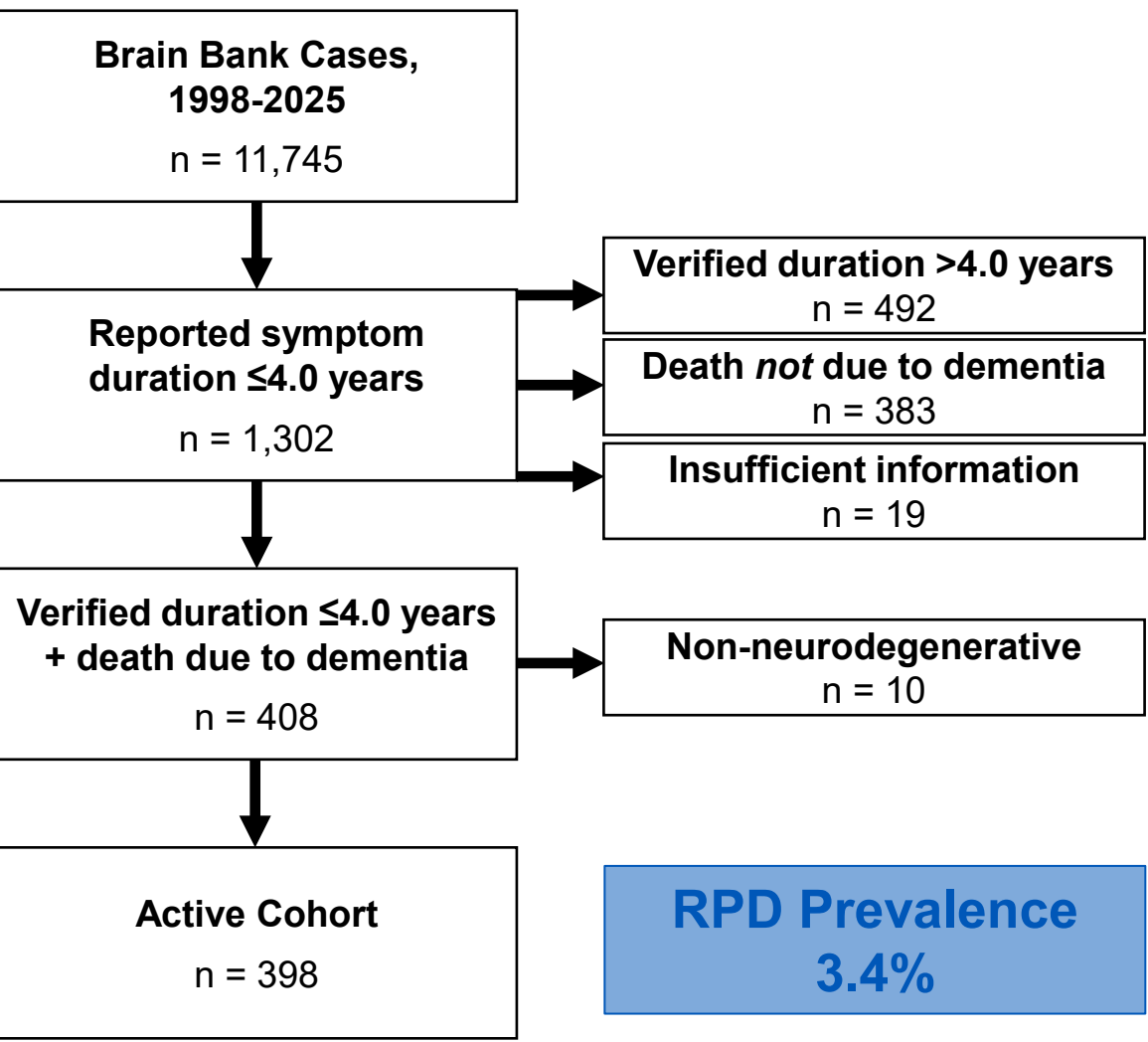
Brain samples were received from North American providers from 1998-2025. Decedent families and providers answered standardized questionnaires and submitted relevant clinical records.

Mayo Clinic Neurodegenerative Brain Bank collected and evaluated brain samples (n=11,745). Patients with ≤4.0 years from symptom-onset to death due to dementia were defined as rapidly progressive.

Neuropathological diagnoses were assigned following standard protocols by neuropathologists.

RESULTS

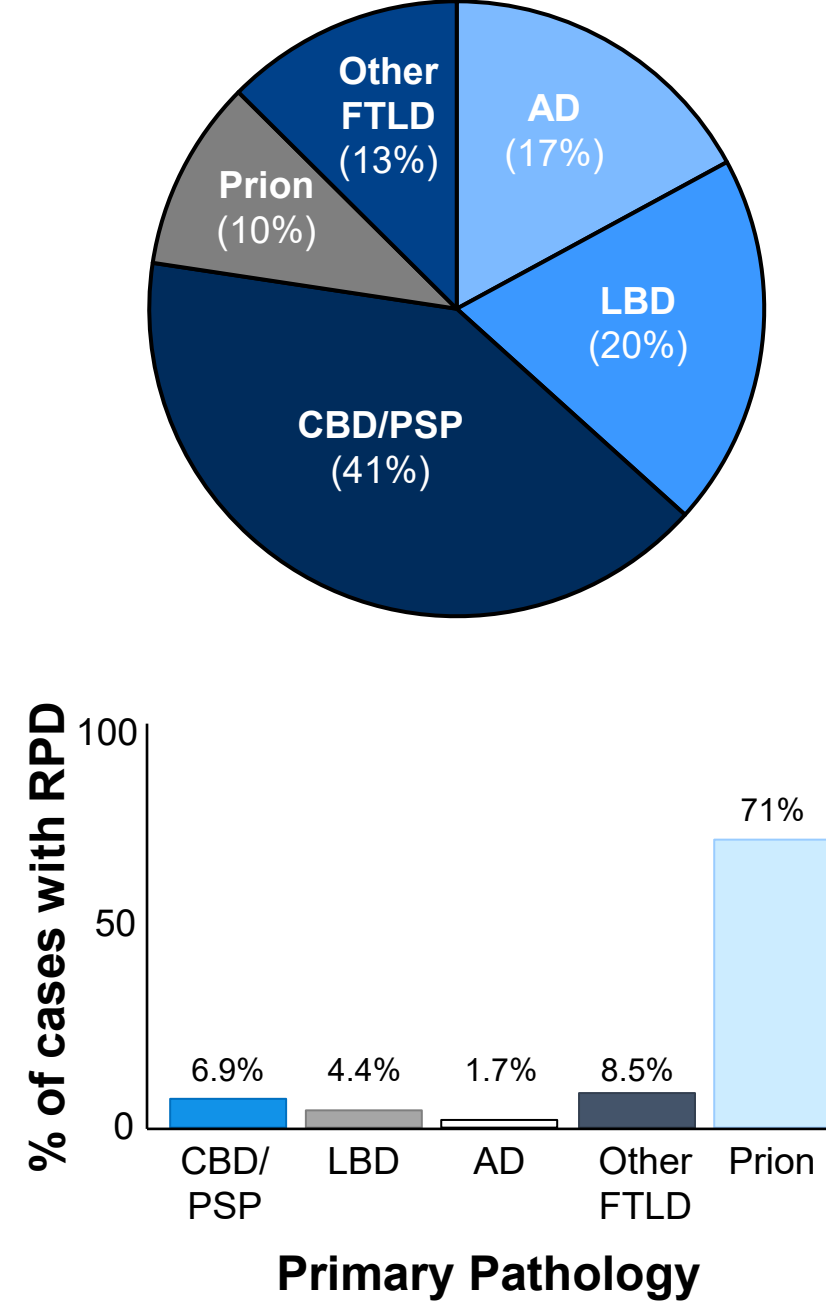
CASE SELECTION & PARTICIPANT CHARACTERISTICS



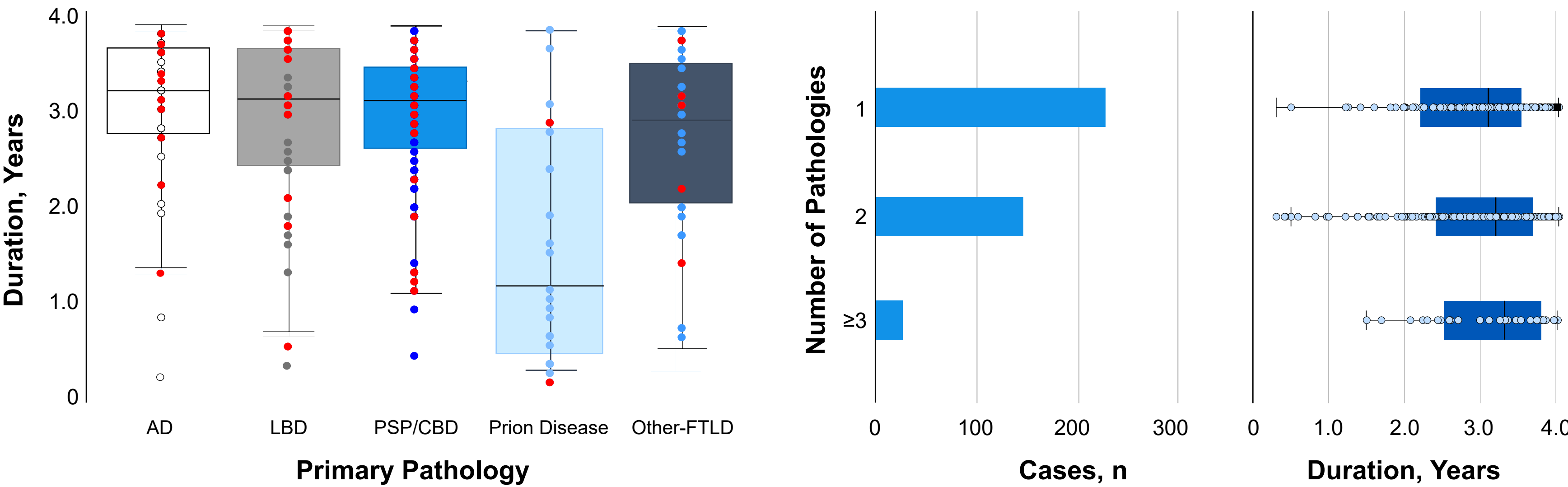
308/11,745 (3.4%) patients in the Mayo Clinic Brain Bank died of dementia attributed to a rapidly progressive neurodegenerative disease.

Participant Characteristics	All RPD (n=398)	Primary Pathology					P Value
		CBD/PSP (n=162)	LBD (n=78)	AD (n=68)	Other FTLD (n=50)	Prion Disease (n=40)	
Age at symptom onset, mean ± SD years	69.2 ± 10.0	69.4 (8.4) ^b	71.6 (6.5) ^{a,b}	73.5 (12.4) ^a	62.6 (11.1) ^d	64.7 (10.3) ^d	<0.001
Disease duration, mean ± SD years	2.9 ± 1.0	3.1 (0.7) ^a	3.0 (0.9) ^a	3.1 (0.8) ^a	2.8 (0.9) ^a	1.4 (1.2) ^b	<0.001
Female sex, n (%)	167 (42.0)	68 (42.0)	26 (33.3)	30 (44.1)	20 (40.0)	23 (57.5)	0.21
Presenting complaint, n (%)							
Cognitive	182 (45.7)	31 (19.1)	46 (59.0) ^a	59 (86.8)	24 (48.0) ^a	22 (55.0) ^a	<0.001
Motor	182 (45.7)	123 (75.9)	26 (33.3) ^a	5 (7.4) ^b	12 (24.0) ^{a,b}	16 (40.0) ^a	<0.001
Behavioral	34 (8.5)	8 (4.9) ^a	6 (7.7) ^a	4 (5.9) ^a	14 (28.0) ^b	2 (5.0) ^{a,b}	<0.001
Additional symptoms and signs, n (%)							
Depression	179/378 (47.4)	67/154 (43.5) ^{a,b}	43/74 (58.1) ^a	30/63 (47.6) ^{a,b}	29/49 (59.2) ^a	10/38 (26.3) ^b	0.008
Hallucinations	117/378 (31.0)	17/151 (11.3) ^a	57/76 (75.0)	15/63 (23.8) ^{a,b}	12/49 (24.5) ^{a,b}	16/39 (41.0) ^b	<0.001
Delusions	121/380 (31.8)	27/154 (17.5) ^a	46/76 (60.5) ^b	25/63 (39.7) ^{b,c}	9/48 (18.8) ^{a,c}	14/39 (35.9) ^{a,b,c}	<0.001
Sleep pathology	175/372 (47.0)	70/155 (45.2) ^{a,b}	47/72 (65.3) ^a	24/60 (40.0) ^b	19/47 (40.4) ^{a,b}	15/38 (39.5) ^{a,b}	0.013

CBD/PSP accounted for most cases of RPD (41%), followed by LBD (20%), AD (17%), other-FTLD (13%) and prion disease (10%). Most patients with prion disease in the Mayo Clinic Brain Bank presented with RPD (40/56, 71%). Patients with rapidly progressive AD or LBD were older. Patients with CBD/PSP were most likely to present with motor complaints. Clinically symptomatic depression, hallucinations, delusions, and sleep disturbances were common across groups, but most common in patients with rapidly progressive LBD.



DOES NEUROPATHOLOGY INFLUENCE SYMPTOMATIC DURATION?



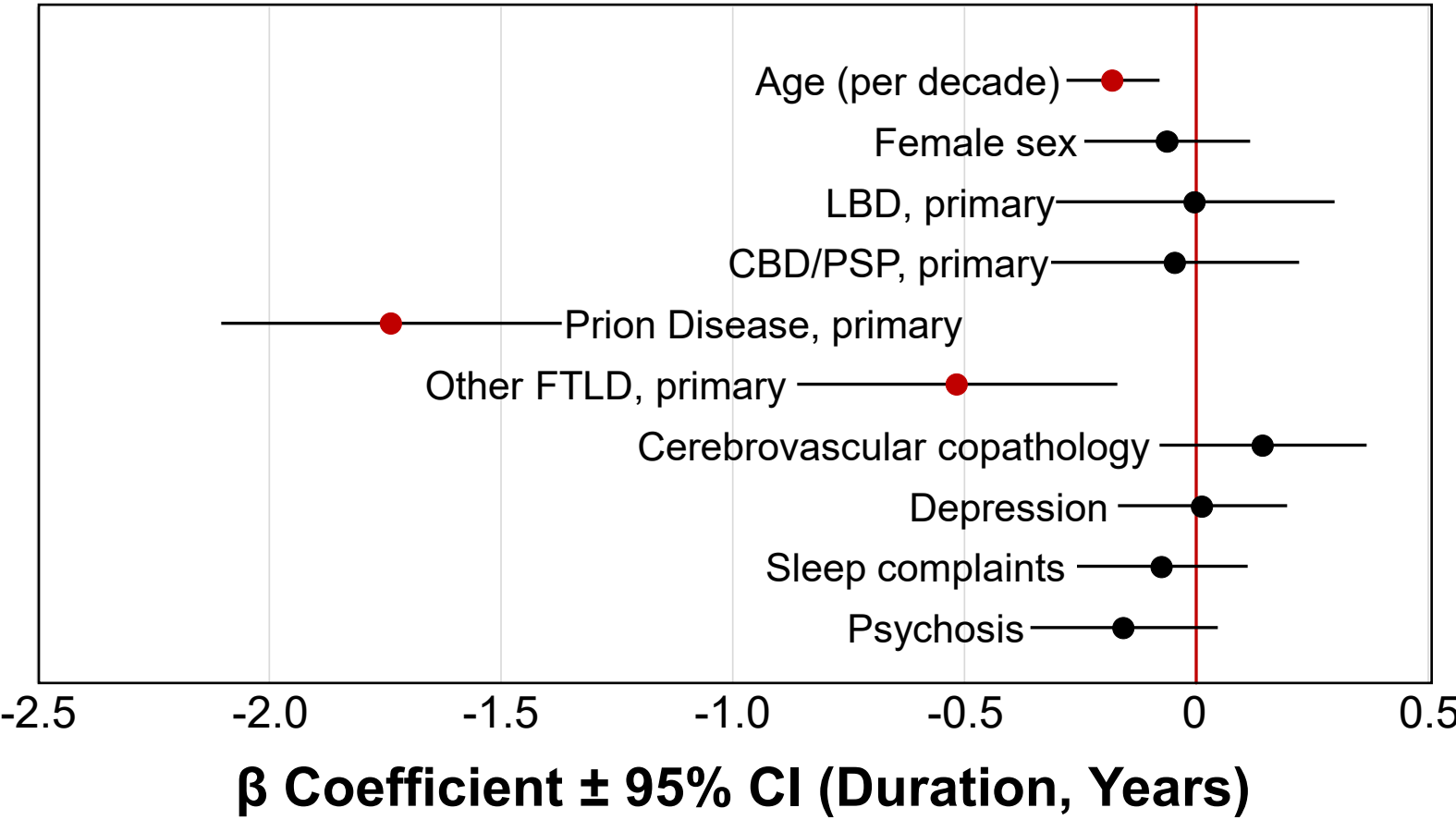
Patients with prion disease experienced the shortest symptomatic duration (p<0.001). No differences in duration were observed across other neurodegenerative diseases. The presence of vascular disease (closed red circles) was not associated with faster progression.

Most patients had a single neuropathological cause of RPD (226/398, 56.8%). 145 patients had two neuropathologies (36.4%)—most commonly CBD/PSP + other FTLD (30.4%) or AD + LBD (27.6%). ≥3 neuropathologies were detected in 27 cases (6.8%). The number of concurrent neuropathologic diagnoses was not associated with symptomatic duration

DO PATIENT CHARACTERISTICS INFLUENCE SYMPTOMATIC DURATION?

Patient-Specific Factors	Duration, Years (Mean ± SD)		P Value
	Present	Absent	
Age ≥75 years	2.76 (0.95)	2.93 (0.99)	0.11
Female sex	2.78 (1.03)	2.96 (0.94)	0.07
APOE ε4 allele carrier*	3.01 (0.73)	3.09 (0.75)	0.43
Depression	2.96 (0.94)	2.83 (1.01)	0.20
Hallucination	2.75 (1.09)	2.94 (0.93)	0.09
Delusions	2.77 (1.08)	2.93 (0.94)	0.13
Psychosis	2.75 (1.10)	2.96 (0.89)	0.04
Sleep complaints	2.87 (0.98)	2.88 (1.00)	0.95
Cerebrovascular disease	3.08 (0.87)	2.82 (1.01)	0.03

Psychoses (hallucinations or delusions) was associated with shorter symptomatic duration, whereas cerebrovascular disease was associated with longer symptomatic duration in univariate analyses. *APOE genotype data available from 218 patients.



In multivariable linear regression, younger age at symptom onset, and primary pathology of prion disease or other FTLD (compared to AD) were independently associated with shorter disease duration. Measured factors accounted for 27% of total variance.

SUMMARY

- RPD accounted for 3.4% of cases in the Mayo Clinic Brain Bank.
- Most cases were attributed to *one* pathology; most often an atypical (rapidly progressive) AD/ADRD.
- Age and selected primary pathologies were independently associated with shorter symptomatic duration.
- Co-pathology (including cerebrovascular disease) and other patient-specific factors exerted minimal effect on symptomatic disease duration.
- The majority of variance in RPD duration remains unaccounted.

CONCLUSIONS

Rapidly progressive presentations of common age-related neurodegenerative diseases accounted for 90% of RPD cases in the Mayo Clinic Brain Bank. These findings highlight the need to consider atypical (rapidly progressive) variants of typical neurodegenerative diseases in patients with RPD.

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