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Biomarker And Pathologic Evidence For Synucleinopathy And Co-pathologies In The Lewy Body Dementias

DLBC

Dementia with Lewy Bodies Consortium

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Background

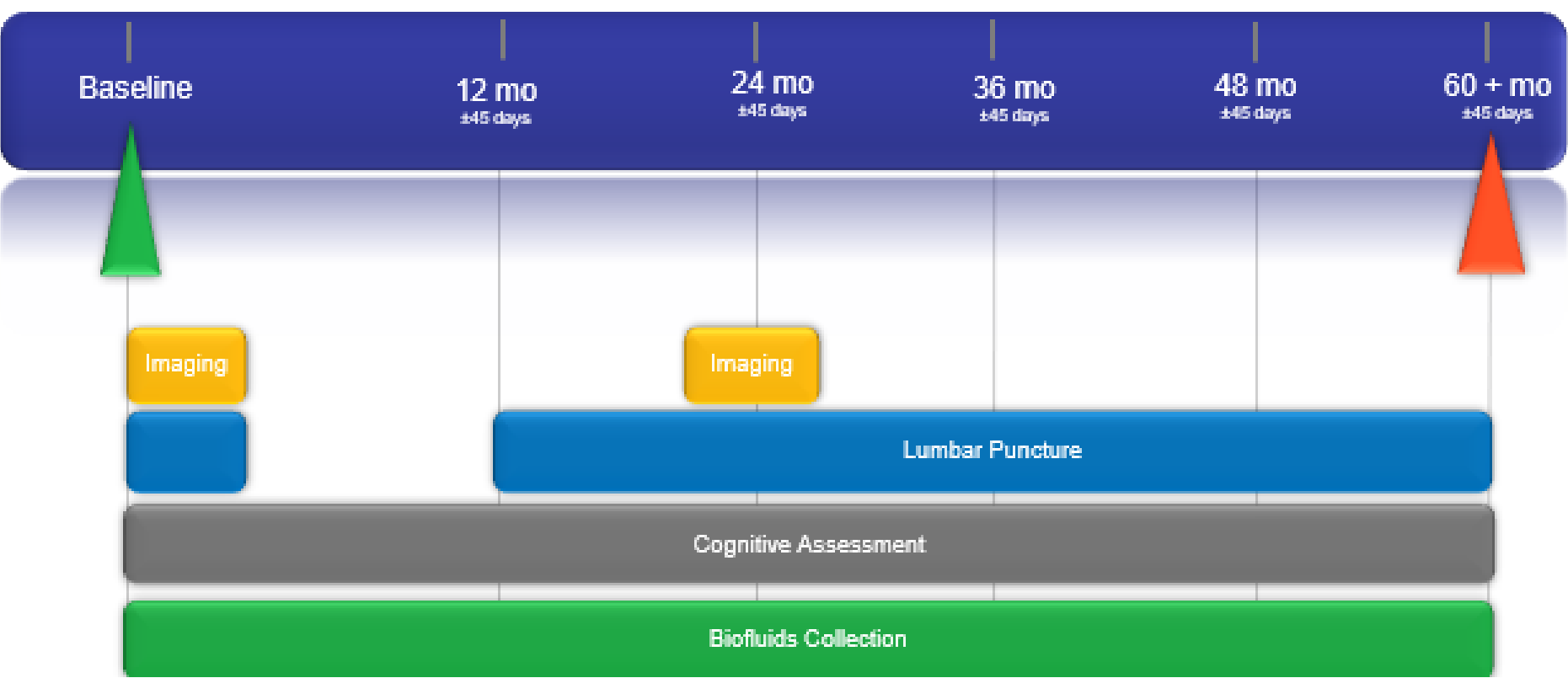
Dementia with Lewy bodies (DLB) is the second most common cause of neurodegenerative dementia and is characterized by progressive cognitive decline accompanied by core clinical features, including cognitive fluctuations (CF), visual hallucinations (VH), and spontaneous parkinsonism. While these features define the clinical diagnosis of DLB, their relationships with dementia severity and longitudinal progression are not well known.



Active Sites: VA-PSHCS, Cleveland Clinic, Johns Hopkins, RUSH, UCSD, UNC, U Penn, U Pittsburgh

Methods

The United States (U.S.) Dementia with Lewy Bodies Consortium (DLBC) is a prospective cohort study conducted across nine sites. Participants (n = 262) underwent standardized cognitive, neuropsychological, and motor assessments at baseline and up to three annual follow-up visits. Dementia severity was measured using the Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) and the Montreal Cognitive Assessment (MoCA). Multiple linear regression models adjusted for age, sex, education, and APOE ε4 status were used to evaluate associations between each DLB core feature and baseline dementia severity. Linear mixed-effects models with random intercepts were used to assess associations between core features and change in dementia severity over time.



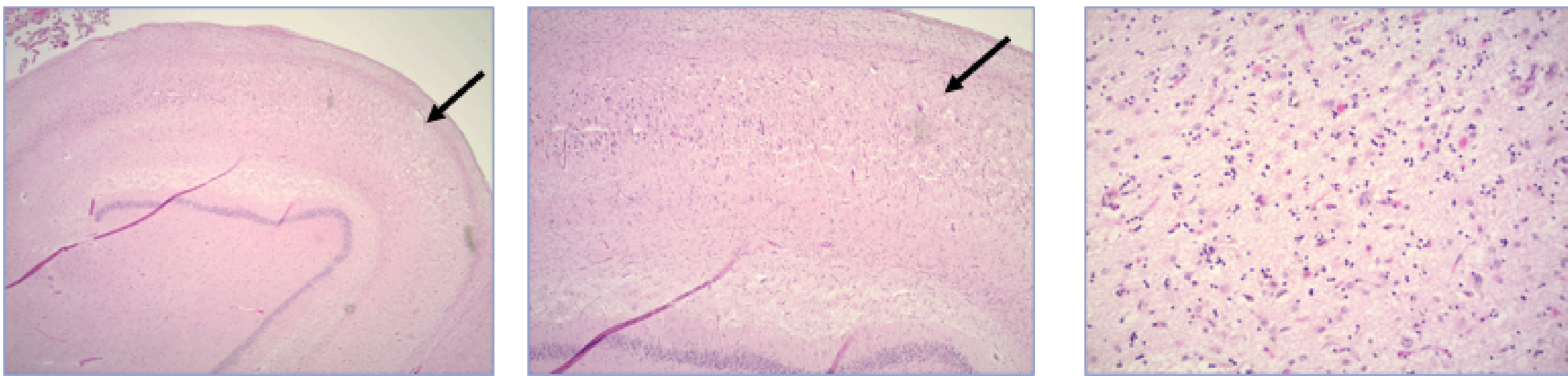
DLBC Full Cohort Characteristics

	N	Mean Score	Median Score	Min Score	Max Score	SD
Age	262	70.95	71	53	89	6.76
Gender-Male	217					
Gender – Female	45					
MoCA BL	262	20.12	21	6	30	5.72
MoCA 12M	151	19.1	21	2	30	6.84
MDS-UPDRS Part III BL	243	25.52	25	0	80	15.5
MDS-UPDRS Part III 12M	144	27.38	25	0	87	17.59

Results

LBD Stage	N	Mean Age	Sex	Mean Time LP to Death (Days)	SAA Pos/Tot
Neocortical	27	70.0 (57-86)	24M/3F	714.4	27/27
Limbic	7	71.6 (62-78)	7M	398.3	7/7
Amygdala Predominant	3	68.3 (63-75)	3M	976.3	1/3
Brainstem Predominant	1	64	1M	246	Indeter
Negative	6	72.7 (67-86)	5M/1F	672.5	0/6
TOTAL	44	70.4	90% M	17.3	35/44

AD and LATE CO-PATHOLOGY						
LBD Stage	N	Mean Age (Range)	ADNC Braak	ADNC Thal	ADNC CERAD	LATE (TDP-43)
Neocortical	27	76.1 (61-89)	2.9 (II-V)	2.7 (0-5)	0.7 (0-freq)	41% (Stage 1-3)
Limbic	7	74.6 (65-83)	2.6 (II-III)	2.6 (0-4)	0.1 (0-1)	14% (Stage 2)
Amygdala Predominant	3	73.0 (66-80)	6.0 (VI)	5.0 (5)	3 (frequent)	66% (Stage 1-2)
Brainstem Predominant	1	66	2 (II)	1	0	0
Negative	6	73 (67-86)	4.0 (II-VI)	1.83 (0-5)	0.83 (0-3)	3/6
TOTAL	44					



LBD (Neocortical); AD Intermediate (A2B2C1) LATE Stage 3/HS

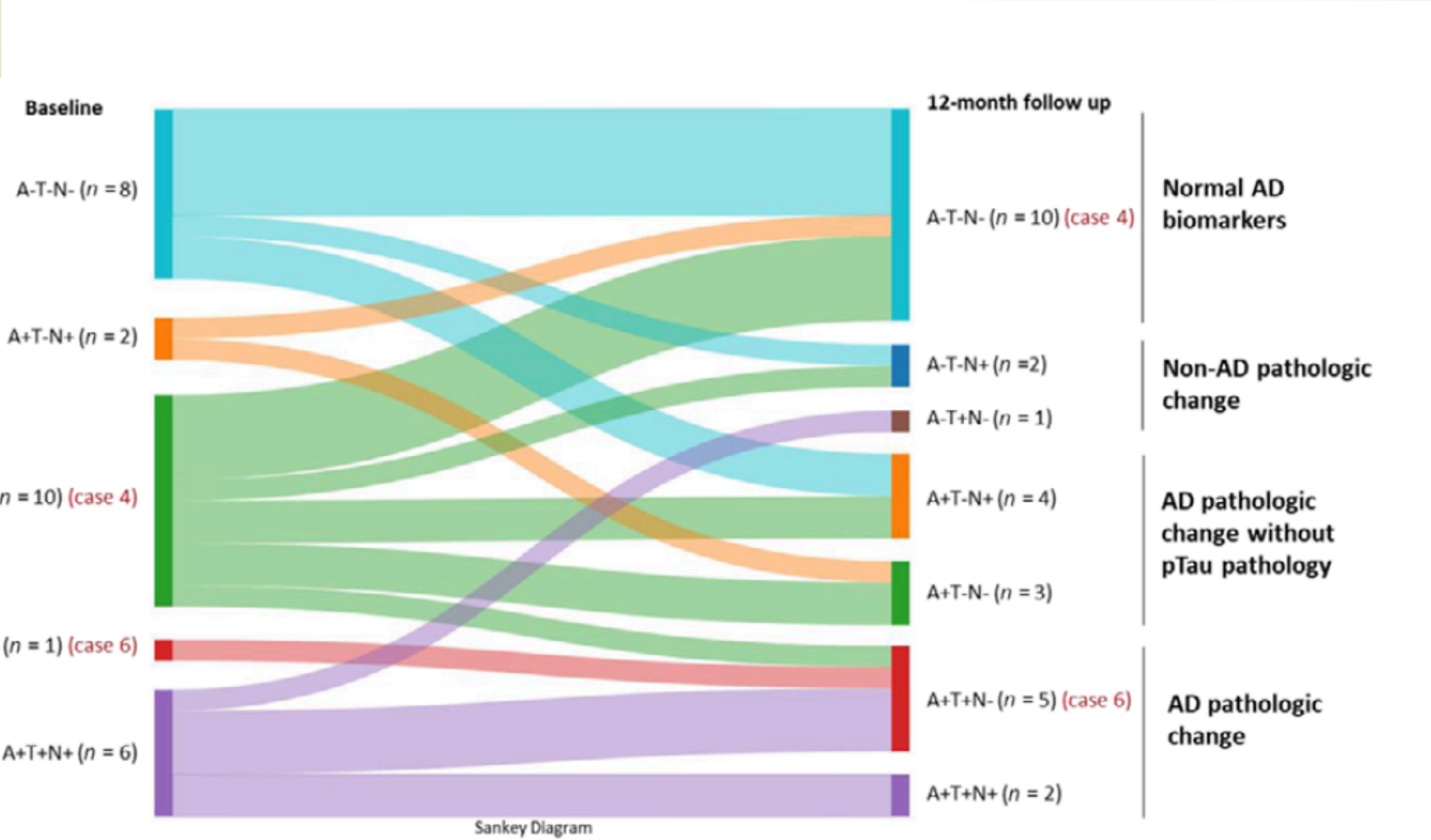
SAA+, Aβ42/40 0.09, pTau 181 84.5 pg/ml, tTau 327.7 pg/ml

*Limbic Predominant Aging-Associated TDP-43 Encephalopathy (LATE)

UO1NS100610

Case no.	Pre-mortem Dx	Post-mortem Dx	PMI	Time from baseline LP to death	Thal stage	Braak Stage	CERAD Score	ABC score	Aβ40	Aβ42	Aβ42/40	p-Tau 181	t-Tau	ATN status
1	DLB	(limbic)	42.85	569days	1	III	absent	A1B2C0	1105	155	0.140271493	36.52	420.93	A-T-N-
2	DLB	(neocortical)	80.75	82days	1	II	absent	A1B1C0	293.92	52.85	0.179810833	37.51	153.24	A-T-N-
3	DLB	(limbic)	21.50	138days	2	II	absent	A1B1C0	764.81	107.9	0.141080791	37.61	279.27	A-T-N-
4	DLB	(limbic)	50.25	537days	0	III	absent	A0B3C0	663.05	77.94	0.117547696	28.49	214.43	A+T-N-
5	DLB	(limbic)	48.00	30 days	2	III	absent	A1B2C0	1340	144.38	0.107746269	49.97	558.76	A+T-N+
6	DLB	(neocortical)	21.18	1066days	2	II	sparse	A1B1C1	1050	117.93	0.112314286	113.8	351.06	A+T+N-
7	DLB	(Amygdala-Predominant)	40.95	825days	5	IV	frequent	A3B3C3	839.58	40.03	0.047678601	122.9	401.51	A+T+N-
8	DLB	(neocortical)	7.93	28 days	5	IV	sparse	A3B2C1	1758	191.82	0.109112628	157.9	613.27	A+T+N+

Note: Autopsy-related features and corresponding CSF ATN status at baseline clinical visit. Post mortem diagnosis for all cases was DLB. Abbreviations: ABC, amyloid, Braak and CERAD; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; DLB, dementia with Lewy bodies; Dx, diagnosis; LBD, Lewy body disease; LP, lumbar puncture; PMI, post mortem interval.



Discussion

In this deeply phenotyped Lewy Body dementia cohort, the neuropathologic results are remarkable for a wide range of co-pathologies. However, the results suggest CSF SAA performed well with 100% specificity based on neuropathologic confirmation of limbic or neocortical Lewy body neuropathologic change (LBNC). False negatives were seen in cases with restricted distribution of LBNC, that is amygdala predominant or brainstem only. Alzheimer's disease (AD) biomarkers also performed well and were notable for early variable changes in Ab pathology and subsequent tau abnormalities, the latter when a higher stage AD neuropathologic change was present. Frequent TDP-43 pathology and less frequent associated hippocampal sclerosis were also observed and emphasize the need for LATE biomarkers.

References

1. Concha-Marambio, L et al, Nat Protoc, 2023. 2. Coughlin D, et al, Neurology, 2024. 3. Coughlin D, et al, Neurology, 2025. 4. Jain L, et al, Alzheimers Dement, 2024 5. Maly EF, et al, Alzheimer Dement, 2025.

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