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BIOMARKERS

PODIUM PRESENTATION

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BIOMARKERS (NON-NEUROIMAGING)

Biological characterization with CSF proteomics of dementia with Lewy bodies (DLB) according Alzheimer's disease (AD) biomarker profile

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Abstract

Background: In dementia with Lewy bodies (DLB), Alzheimer co-pathology is common, and associated with an unfavorable prognosis. For targeted treatment development it is crucial to understand the biological underpinnings of DLB with Alzheimer co-pathology, and how it differs from Alzheimer disease (AD). We performed a cerebrospinal fluid (CSF) proteome profiling to biologically characterize DLB with and without AD co-pathology *in vivo*.

Method: Patients from Amsterdam Dementia Cohort, Twin60+, and UPENN, we selected individuals with DLB (n=109), and subcategorized them in CSF $A\beta_{42}$ (A-/A+) and pTau-181 (T-/T+) biomarker groups (A-T- n=29; A-T+ n=16; A+T- n=29; A+T+ n=36), and patients with AD dementia (A+T+ n=230) and cognitively normal controls (A-T- n=246). CSF levels of 810 proteins were measured with the Olink proximity extension assay. We compared protein profiles from the DLB subgroups and AD dementia with controls with ANCOVA adjusted for age and sex. Proteins with significant FDR-controlled p-values were used to perform functional enrichment analyses in KEGG and GO Biology and Cellular components using STRING-DB.

Result: DLB A-T- exhibited least abnormalities compared to controls, with 6 proteins dysregulated (Figure 1). DLB A-T+ had 12 upregulated proteins. DLB A+T- exhibited the most distinct protein dysregulation, with 16 upregulated proteins, and 312 downregulated proteins. DLB A+T+ had 3 downregulated and 18 upregulated proteins. Of the DLB groups, DLB A+T+ had with 15 proteins the largest overlap in dysregulated proteins with AD dementia patients (Figure 1). In functional enrichment analysis for DLB A-T- no enrichment was present. DLB A-T+ and DLB A+T+ groups were enriched for proteins involved cytokine-cytokine interactions. The DLB A+T- group had top enrichment for basement membrane components and phenylalaline

metabolism upregulation, and cell adhesion molecules, VEGF, and axon guidance and morphogenesis downregulation.

Conclusion: The CSF proteome in DLB varied depending on the CSF AD profile. The overlap in CSF proteome between AD dementia and DLB with signs of AD seems to cover mostly immune-mediated processes. The biological abnormalities in DLB with isolated abnormal CSF Aβ_{42} were most distinct, possibly pointing to a unique subtype. Using biomarkers and proteomics for understanding the biology behind AD co-pathology could guide treatment development for DLB.

Table 1 Patient characteristics

	DLB N=109	DLB Subgroups				AD dementia N=230	Controls N=246
Characteristics		DLB A-T- N=29	DLB A-T+ N=16	DLB A+T- N=29	DLB A+T+ N=36		
Age, years	69 (8)	66 (7)	69 (9)	71 (6)	71 (9)	66 (8)	60 (8)
Male, n (%)	91 (83%)	26 (90%)	14 (88%)	24 (83%)	27 (77%)	135 (59%)	148 (60%)
MMSE, median±IQR	23 ± 6	23 ± 4	24 ± 5	23 ± 7	22 ± 10	21 ± 7	29 ± 2

DLB = Dementia with Lewy bodies; MMSE = mini-mental state examination; Missingness: MMSE N=11.

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Figure 1 Protein dysregulation in DLB and overlap with AD dementia

A Expression compared to Controls and overlap with AD dementia

	DLB A-T-		DLB A-T+		DLB A+T-		DLB A+T+	
	4 ↑	2↓	12↑	0 ↓	16 ↑	296 ↓	18 ↑	3 ↓
384 ↑ in AD	3	0	11	-	7	140	15	0
13 ↓ in AD	0	0	0	-	1	3	0	0

B 28 proteins with increased or decrease expression compared to controls in both one or more DLB groups and AD dementia