

Age-Related Differences in Cognitive Profile and CSF Biomarkers in Alzheimer's Disease

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Background: Alzheimer's disease (AD) can be classified into two subtypes based on the age of symptom onset: early-onset AD (EOAD, <65 years) and late-onset AD (LOAD, >65 years). Though both forms share core neuropathological features, they often differ in their clinical presentation, genetic background and progression. EOAD tends to have a more aggressive course, with prominent impairments in non-memory cognitive domains such as language, visuospatial function, or executive skills, while LOAD more commonly presents with predominant episodic memory deficits. We aimed to assess associations between cognitive profile and CSF biomarkers of AD patients according to age at onset.

Methods: We consecutively recruited 277 subjects with clinical-biological diagnosis of AD (206 MCI due to AD, 71 AD dementia). We classified them in three groups based on age at onset: I) EAOD (68); II) LOAD, 65-74 years (143); III) very late-onset AD (VLOAD), >75 years (66). All subjects underwent lumbar puncture for CSF analysis and an extensive neuropsychological assessment.

Results: EOAD were more impaired in non-memory cognitive domains (see Tab.1). Conversely, LOAD and VLOAD showed greater impairment in a verbal episodic memory test. LOAD and VLOAD presented the same neuropsychological profile, without significant differences. Linear regression analyses accounting for cognitive severity and demographics revealed how age at onset was an independent predictor of impairment for RAVLT delayed recall, Spatial Span Forward, Spatial Span Backward, MFTC time, ROCF copy. LOAD and VLOAD demonstrated higher levels of amyloidopathy relative to EOAD. Neuropsychological scores were not predicted by CSF biomarkers in EOAD group. In LOAD, CSF $\alpha\beta 42$ levels were primary associated with poorer performance across multiple cognitive domains, whereas CSF t-tau and p-tau concentrations were the strongest predictors of cognitive performance in VLOAD (see Tab 2.).

Conclusion:

Different spatial pattern of neurodegeneration may explain our findings: hippocampal and medial temporal atrophy is more reported in LOAD, while atrophy of the caudal-lateral temporal cortex, posterior cingulate and precuneus cortices, and inferior parietal lobule is typical of EOAD. On the other hand, the prominent episodic memory deficit emerged in older patients may be partially explained by the presence of focal temporal copathologies such as LATE or PART.

Overall, our results highlight the importance of considering a broader range of cognitive symptoms – beyond memory complaints – particularly in younger population, where there's higher prevalence of atypical presentations. Furthermore, our results suggest that CSF biomarkers may present different associations with cognitive performance in different age ranges.

Tab.1: CSF biomarkers and neuropsychological tests

	1. EOAD	2. LOAD	3. VLOAD	p-value
$\alpha\beta 42$	499	514	547	1vs2*; 1vs3**
$\alpha\beta 42/40$	0.049	0.046	0.044	1vs2*; 1vs3*
p-tau	113	121	122	
t-tau	725	772	789	
MMSE	22.2	23.4	24.5	1vs2*; 1vs3**
RAVLT imm. recall	21.1	21.6	20.8	
RAVLT del. recall	2.2	1.5	1.6	1vs2*; 1vs3*
DS Forward	4.9	5.1	5.4	1vs3*
DS Backward	2.8	3.1	3.3	
SS Forward	3.4	3.8	4.1	1vs2*; 1vs3**
SSI Backward	2.3	3.0	3.2	1vs3**
Raven	17.9	20.0	21.4	1vs3*
MFTC accuracy	0.80	0.86	0.81	1vs2*
MFTC time	120	98	89	1vs2*; 1vs3**
TMT-A	120	99	98	
TMT-B	258	223	242	1vs2*
Phonological fluency	22.0	25.0	23.7	
Semantic fluency I	9.5	10.4	9.7	
Semantic fluency II	22.1	22.8	20.6	
Denomination task	24.0	24.7	25.5	
ROCF copy	17.3	23.3	23.5	1vs2**; 1vs3*
ROCF memory	3.9	3.4	4.3	

*= $p < 0.05$; **= $p < 0.01$

Tab. 2: significant correlations between CSF biomarkers and tests

EOAD:	
-	
LOAD:	
$\alpha\beta 42$	Spatial Span Forward*, Raven*, TMT-A**, Phonological FT*, ROCF copy*
p-tau	RAVLT imm. recall*
t-tau	RAVLT imm. recall*
VLOAD:	
p-tau	MMSE*, RAVLT imm. recall**, del. recall**, Digit Span Forward*, Raven*, MFTC acc., TMT-A**, TMT-B*, Phonological FT*, Semantic FT I**, II**, Denomination*, ROCF memory**
t-tau	RAVLT imm. recall**, del. recall**, Digit Span Forward*, Raven*, TMT-A**, TMT-B**, Phonological FT*, Semantic FT I**, II**, Denomination*, ROCF memory*

*= $p < 0.05$; **= $p < 0.01$; ***= $p < 0.001$



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