

Biomarker-Negative Limbic-Predominant Neurodegeneration Suggestive of LATE

Reconsideration of Prior Alzheimer Disease and Mixed Vascular Dementia Labels Following Longitudinal Reassessment

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Biomarker-negative amnesic syndromes with progressive hippocampal atrophy may represent probable LATE-pattern neurodegeneration and warrant diagnostic reassessment.

INTRODUCTION

LATE is frequently misclassified as Alzheimer disease or vascular dementia, particularly in highly educated individuals where cognitive reserve masks early impairment. Integration of longitudinal neuroimaging, quantitative volumetry, and plasma biomarker profiling is essential to resolve sustained diagnostic ambiguity in biomarker-negative amnesic syndromes.

DIAGNOSTIC HISTORY (2017–2024)

Probable Alzheimer

2017–2024

Possible Alzheimer

2017–2024

Mixed Vascular Dementia

2017–2024

Plasma ATN Workup 2025

Probable LATE with Vascular Contribution

COGNITIVE TRAJECTORY

23/30 → 18/30

2017 · MCI

2026 · NCD

9 years · Doctoral-level education · Slow progression

LONGITUDINAL TIMELINE

2016

2017

2020

2024

2025

2026

MRI Baseline

SLUMS 23 MCI

Aripiprazole-related parkinsonism

Stopped → resolved

ATN · MRI CPAP

SLUMS 18 Probable LATE

Reviewer Takeaway

Slow amnesic progression with severe hippocampal atrophy and A–T–N– plasma profile supports reconsideration of Alzheimer labels.

METHODS

A highly educated older woman carrying prior diagnoses of probable Alzheimer, possible Alzheimer, and mixed vascular dementia underwent longitudinal SLUMS assessment, serial MRI with quantitative volumetric analysis using AIRAScore (AIRAmed; FDA 510(k) cleared; institutional pilot, non-billed) confirmed by independent neuroradiological review, and plasma ATN profiling using Fujirebio Lumipulse and Roche ECLIA platforms.

Assay methods: Aβ42/40 Sysmex CLEIA · p-tau181/NfL Roche ECLIA · p-tau217 Fujirebio Lumipulse CLEIA

Interpreted using platform-specific reference ranges.

SERIAL NEUROIMAGING 2016 → 2025

Panel A · 2016 Baseline · T1 Coronal

Panel B · 2025 MPRAGE · 1mm Coronal

Panel C · 2017 FLAIR · Baseline WMH

Panel D · 2025 FLAIR · Progression

MRI VISUAL RATING SCORES

4	1	2	3	2
MTA	Koedam	GCA	ERICA	Fazekas

Fazekas 1 → Fazekas 2 (2017→2025) | not dominant etiology

RESULTS

Cognition

- SLUMS declined from 23/30 to 18/30 over nine years with disproportionate episodic memory impairment (delayed recall 0/5), preserved attention, and mild executive dysfunction.

Domain	2017	2026	Trend
Delayed Recall	3/5	0/5	↓↓↓ Severe
Attention	2/2	2/2	↔ Preserved
Clock Draw	2/4	2/4	↓ Mild
Story Recall	8/8	6/8	↓ Mild
Orientation	3/3	Partial	↓ New

MRI / Volumetry

- Progressive bilateral hippocampal atrophy at the 0th percentile bilaterally on age- and sex-adjusted normative comparison.
- Ex-vacuo ventricular enlargement at the 99.9th percentile.
- Posterior cortical architecture preserved throughout.
- White matter progression (Fazekas 1 to 2).

AIRAScore Quantitative Volumetry

	Absolute Volume in ml	Relative Volume in %TV (Percentile)
Ventricles		
Lateral ventricle (L)	32.4	2.5 (95.3)
Lateral ventricle (R)	38.7	2.9 (99.9)
3rd ventricle	4.03	0.31 (100.0)
4th ventricle	2.98	0.23 (98.7)
Brain Lobes (Gray Matter)		
Frontal (L)	53.9	4.1 (1.8)
Parietal (L)	35.1	2.7 (5.3)
Occipital (L)	15.7	1.2 (6.8)
Temporal (L)	35.6	2.7 (6.6)
Insula (L)	4.9	0.4 (2.3)
Frontal (R)	54.8	4.2 (2.3)
Parietal (R)	36.9	2.8 (9.3)
Occipital (R)	17.4	1.3 (14.2)
Temporal (R)	33.7	2.6 (3.1)
Insula (R)	5.1	0.4 (9.2)
Limbic Lobe		
Hippocampus (L)	1.02	0.08 (0.0)
Hippocampus (R)	1.08	0.08 (0.0)

Hippocampus L: 0th (1.02 ml)
Hippocampus R: 0th (1.08 ml)
Ventricle R: 99.9th (38.7 ml)
Post. Cortex: Intact (Koedam 1)

RESULTS

Differential Diagnosis

1 LATE — Limbic Neurodegeneration Most Likely

2 Mixed Vascular Cognitive Impairment Contributing

3 Limbic Lewy / Parkinsonian Spectrum Possible

X Alzheimer Disease — ATN A–T–N– Argues Against

Plasma Biomarker Platforms

☐ Aβ42/40: Sysmex CLEIAp-tau181

☐ Roche Diagnostics ECLIAp-tau217

☐ Fujirebio Lumipulse CLEIA

CONCLUSION

Multimodal reassessment argued against three concurrent dementia diagnoses sustained over seven years and revealed severe limbic-predominant neurodegeneration with negative Alzheimer plasma biomarkers. The pattern is most consistent clinically with a biomarker-negative LATE-pattern syndrome with vascular contribution.

Interpretive caution:

LATE remains a clinicopathologic diagnosis; absence of CSF, amyloid PET, tau PET, or neuropathologic confirmation limits definitive classification.

ACCEPTED ABSTRACT — VERBATIM CONCLUSION

"Multimodal evaluation arguing against three concurrent dementia diagnoses sustained over seven years reveals limbic-predominant neurodegeneration with hippocampal atrophy at the 0th percentile and negative Alzheimer biomarkers across two independent platforms, most consistent with probable LATE with vascular contribution. This case highlights the urgent need for systematic plasma ATN biomarker integration in patients carrying unconfirmed dementia diagnoses, as biomarker-negative amnesic syndromes may represent LATE requiring distinct prognostic and management pathways."

CLINICAL IMPLICATIONS

Progressive amnesic syndromes with negative plasma AD biomarkers should prompt consideration of non-Alzheimer neurodegenerative etiologies.

Serial MRI and quantitative volumetry may reveal progressive neurodegeneration despite negative plasma AD biomarkers.

Avoid diagnostic anchoring to Alzheimer disease when structural neurodegeneration and clinical progression are discordant with biomarker findings.

LIMITATIONS

Single-patient observational case.

Plasma biomarkers may not capture all neurodegenerative pathologies.

Neuropathological confirmation unavailable.

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