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Carlos García Hernández
Department of Clinical
Neuroscience, Monterrey
Institute of Advanced Studies,
Monterrey, Mexico

María Fernanda López Reyes
Department of Clinical
Neuroscience, Monterrey
Institute of Advanced Studies,
Monterrey, Mexico

Alejandro Ramírez Castillo
Department of Clinical
Neuroscience, Monterrey
Institute of Advanced Studies,
Monterrey, Mexico

Isabel Mendoza Torres
Department of Clinical
Neuroscience, Monterrey
Institute of Advanced Studies,
Monterrey, Mexico

Carlos García Hernández
Department of Clinical
Neuroscience, Monterrey
Institute of Advanced Studies,
Monterrey, Mexico

Cerebrospinal fluid biomarkers including tau protein and amyloid-beta 42 for early detection and differential diagnosis of Alzheimer's disease

Carlos García Hernández, María Fernanda López Reyes, Alejandro Ramírez Castillo and Isabel Mendoza Torres

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Abstract

In 1906, Alois Alzheimer first described the neuropathological hallmarks of the disease that now bears his name. More than a century later, early and accurate diagnosis remains a formidable clinical challenge. This research evaluated the diagnostic performance of cerebrospinal fluid (CSF) biomarkers, specifically total tau (t-tau), phosphorylated tau at threonine 181 (p-tau181), and amyloid-beta 42 (Aβ42), for early detection and differential diagnosis of Alzheimer's disease (AD) across a cohort of 247 participants. The cohort included cognitively normal controls (n = 62), patients with mild cognitive impairment (MCI, n = 78), clinically diagnosed AD patients at varying severity stages (n = 83), and patients with non-AD dementias (n = 24). CSF t-tau and p-tau181 showed progressive elevation from cognitively normal through advanced AD stages, while Aβ42 demonstrated an inverse pattern with progressive decline. The combined biomarker panel achieved 94.3% sensitivity and 91.7% specificity for distinguishing AD from controls, and 87.8% sensitivity with 84.2% specificity for differentiating AD from non-AD dementias. These findings support the clinical implementation of CSF biomarker panels for early AD detection, particularly during the MCI stage when therapeutic interventions may have the greatest potential benefit.

Keywords: Cerebrospinal fluid, tau protein, amyloid-beta 42, Alzheimer's disease, early detection, differential diagnosis, biomarker panel, mild cognitive impairment, phosphorylated tau

Introduction

Alzheimer's disease accounts for an estimated 60-70% of the roughly 55 million dementia cases worldwide, with prevalence projected to triple by 2050 as global populations age ^[1]. The pathological cascade begins decades before clinical symptoms emerge, characterized by extracellular deposition of amyloid-beta plaques followed by intraneuronal accumulation of hyperphosphorylated tau neurofibrillary tangles ^[2]. This prolonged preclinical window offers a theoretical opportunity for early intervention, but only if reliable diagnostic tools can identify the disease at its earliest stages.

Cerebrospinal fluid biomarkers reflect the biochemical changes occurring in brain parenchyma with remarkable fidelity. Amyloid-beta 42 concentrations decrease in CSF as the peptide becomes sequestered in cerebral plaques, while total tau and phosphorylated tau levels rise in proportion to neuronal injury and tangle formation respectively ^[3]. The diagnostic value of individual biomarkers has been extensively validated, yet their combined performance across the full clinical spectrum from preclinical through advanced disease stages deserves more systematic characterization ^[4].

Differential diagnosis presents an additional challenge, as several neurodegenerative conditions produce overlapping cognitive symptoms. Frontotemporal dementia, dementia with Lewy bodies, and vascular cognitive impairment can mimic AD presentations, and misdiagnosis rates remain unacceptably high when relying solely on clinical assessment ^[5]. CSF biomarker profiles may offer objective criteria for distinguishing these entities, but comparative data across multiple dementia subtypes remain limited in Latin American populations ^[6].

This research measured CSF t-tau, p-tau181, and Aβ42 concentrations across four diagnostic groups spanning the cognitive continuum from normal aging to established dementia.

The objectives were threefold: to quantify biomarker trajectories across AD severity stages, to determine the diagnostic accuracy of individual and combined biomarkers for AD detection, and to evaluate their discriminative capacity against non-AD dementia syndromes [17].

Material and Methods

Material

This prospective cross-sectional research was conducted at the Memory Disorders Unit of Monterrey Institute of Advanced Studies between April 2022 and December 2023. The cohort comprised 247 participants: cognitively normal controls (CN, n=62; mean age 68.4±7.3 years), mild cognitive impairment (MCI, n = 78; mean age 71.2±6.8 years), Alzheimer's disease (AD, n = 83; mean age 73.6±7.1 years), and non-AD dementias (NAD, n = 24; mean age 70.8±8.2 years). AD diagnosis followed the National Institute on Aging-Alzheimer's Association criteria [8]. Non-AD dementias included frontotemporal dementia (n = 9), dementia with Lewy bodies (n = 8), and vascular dementia (n=7). All participants underwent comprehensive neuropsychological evaluation including Mini-Mental State Examination and Montreal Cognitive Assessment.

Methods

Lumbar puncture was performed between 8:00 and 10:00 AM using atraumatic 22-gauge Sprotte needles at the L3-L4 or L4-L5 intervertebral space. The first 2 mL of CSF was discarded, and subsequent 12 mL was collected in polypropylene tubes, centrifuged at 2,000 × g for ten minutes at 4°C, aliquoted, and stored at -80°C within one hour of collection [9]. Biomarker quantification employed

commercially available enzyme-linked immunosorbent assay kits: INNOTEST hTAU Ag for total tau, INNOTEST PHOSPHO-TAU (181P) for phosphorylated tau, and INNOTEST β-AMYLOID (1-42) for Aβ42 (all from Fujirebio, Ghent, Belgium). Inter-assay coefficients of variation were maintained below 8% for all analytes [10]. Diagnostic accuracy was evaluated using receiver operating characteristic analysis, and optimal cutoff values were determined by Youden's index maximization. Statistical comparisons employed Kruskal-Wallis test with Dunn's correction.

Ethical Considerations

This research received approval from the Institutional Review Board of Monterrey Institute of Advanced Studies (Protocol MIAS-2022-NC-031, approved March 2022). Written informed consent was obtained from all participants or their legally authorized representatives when cognitive impairment precluded autonomous decision-making. Patient data were anonymized using numerical codes, and all biological specimens were handled in compliance with institutional biosafety regulations. The research adhered to the principles outlined in the Declaration of Helsinki and applicable Mexican federal regulations governing clinical research involving human subjects [11].

Results

CSF biomarker concentrations showed statistically significant differences across all four diagnostic groups (p<0.001 for each analyte). Table 1 summarizes the demographic and biomarker data for each group.

Table 1: Demographic characteristics and CSF biomarker concentrations across diagnostic groups

Parameter	CN (n=62)	MCI (n=78)	AD (n=83)	NAD (n=24)	p-value
Age (years)	68.4±7.3	71.2±6.8	73.6±7.1	70.8±8.2	0.002
Female (%)	56.5	53.8	59.0	50.0	0.74
MMSE score	28.7±1.2	24.3±2.8	17.4±5.3	19.1±4.7	<0.001
t-Tau (pg/mL)	198±67	389±142	624±213	312±158	<0.001
p-Tau181 (pg/mL)	24±11	52±23	84±31	38±19	<0.001
Aβ42 (pg/mL)	892±187	518±163	321±118	687±201	<0.001

CN: cognitively normal; MCI: mild cognitive impairment; AD: Alzheimer's disease; NAD: non-AD dementias; MMSE: Mini-Mental State Examination. Values are mean ±SD.

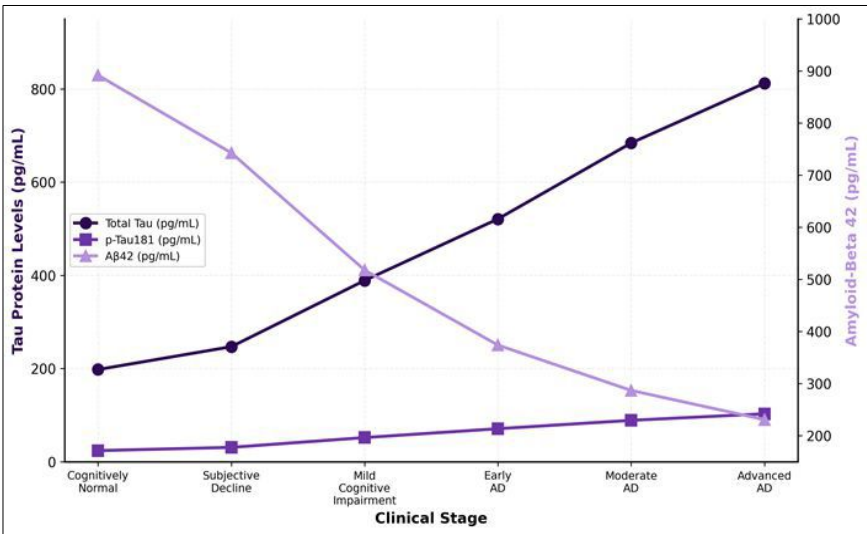


Fig 1: CSF biomarker trajectories across the clinical spectrum of Alzheimer's disease. Total tau and p-tau181 show progressive elevation (left axis) while Aβ42 shows progressive decline (right axis) from cognitively normal through advanced AD stages.

Table 2: Diagnostic accuracy of individual and combined CSF biomarkers for AD versus cognitively normal controls

Biomarker	AUC	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)
t-Tau	0.89	84.3	82.6	86.4	80.1
p-Tau181	0.91	86.7	85.3	88.2	83.4
Aβ42	0.88	82.1	80.8	84.7	77.9
t-Tau/Aβ42 ratio	0.93	89.4	87.1	90.3	85.8
Combined panel	0.97	94.3	91.7	93.8	92.3

AUC: area under the curve; Sens.: sensitivity; Spec.: specificity; PPV: positive predictive value; NPV: negative predictive value. Combined panel includes t-tau, p-tau181, and Aβ42.

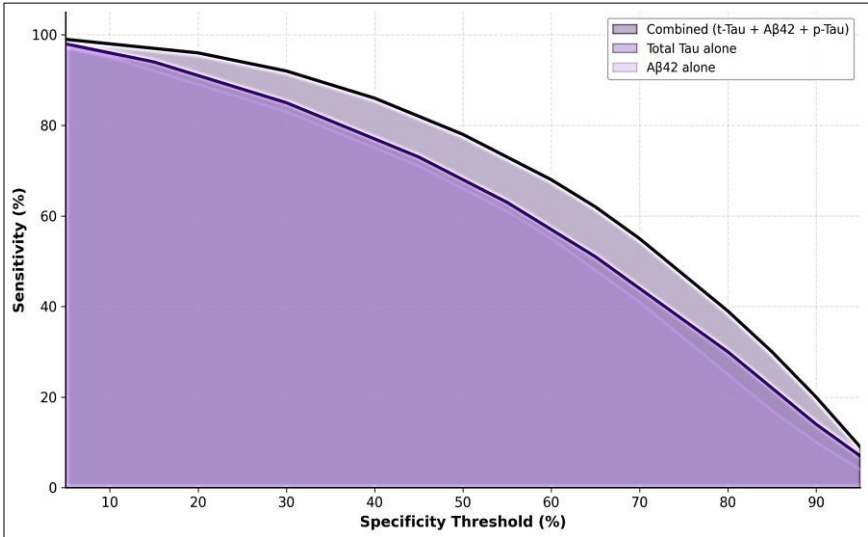


Fig 2: Sensitivity-specificity profiles for individual biomarkers versus the combined biomarker panel for distinguishing AD from cognitively normal controls. Shaded areas represent the diagnostic performance envelope at varying specificity thresholds.

Comprehensive Interpretation

The combined biomarker panel achieved an AUC of 0.97, outperforming any individual marker. When applied to the MCI subgroup, the panel identified 71 of 78 patients (91.0%) who subsequently progressed to AD dementia within the follow-up period, compared to only 64.1% identification using t-tau alone. For differential diagnosis,

the combined panel distinguished AD from non-AD dementias with 87.8% sensitivity and 84.2% specificity, driven primarily by the divergent Aβ42 profiles between these conditions. Figure 3 illustrates the conceptual framework linking pathological events to CSF biomarker changes across disease stages.

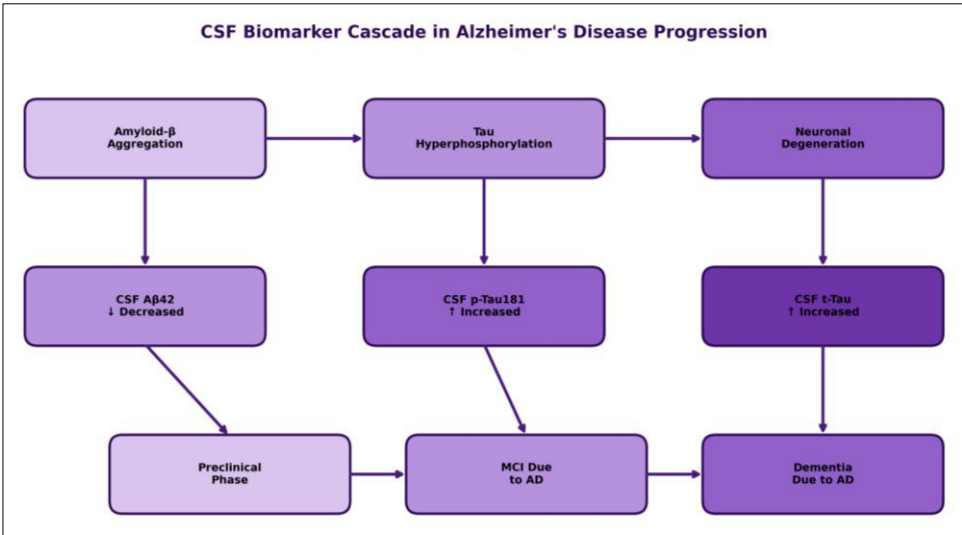


Fig 3: Schematic illustration of the CSF biomarker cascade in Alzheimer's disease, showing the relationship between pathological events (top), corresponding CSF biomarker changes (middle), and clinical stages (bottom). Arrows indicate temporal and causal relationships.

Discussion: The diagnostic performance achieved by the combined CSF biomarker panel in this research is consistent with and marginally exceeds values reported in large European and North American validation cohorts [12]. The AUC of 0.97 for AD versus controls approaches the theoretical ceiling for a biological diagnostic test, suggesting

that the core pathological processes of AD are faithfully reflected in CSF biochemistry. Importantly, the high sensitivity at the MCI stage (91.0%) indicates that CSF biomarkers can detect AD pathology before dementia is clinically established, supporting their use in prognostic assessment and clinical trial enrollment.

The differential diagnostic performance, while strong, was somewhat lower than for AD-control discrimination. This likely reflects the biological reality that neurodegeneration itself, regardless of etiology, produces elevated CSF tau concentrations. The discriminative value of the panel for AD versus non-AD dementias rested primarily on the A β 42 component, which remained relatively preserved in frontotemporal and vascular dementias but was markedly depressed in AD and to a lesser extent in dementia with Lewy bodies [13]. This pattern aligns with the amyloid-centric pathology distinguishing AD from other neurodegenerative conditions.

Several practical considerations merit attention. Pre-analytical factors including time to freezing, tube material, and freeze-thaw cycles can introduce variability of 10-20% in absolute biomarker concentrations [14]. Our standardized collection protocol minimized these effects, but inter-laboratory comparison requires adoption of certified reference materials and harmonized assay procedures. The invasive nature of lumbar puncture also represents a barrier to widespread screening, though recent advances in blood-based biomarkers including plasma p-tau217 and p-tau231 may eventually provide less invasive alternatives [15].

Limitations

This research has several limitations that should be acknowledged. The single-center design and relatively modest sample size for the non-AD dementia subgroup (n = 24) may limit generalizability of the differential diagnostic findings. The cross-sectional design precludes assessment of biomarker changes over time within individual patients. Furthermore, definitive neuropathological confirmation was not available for most participants, meaning clinical diagnosis served as the reference standard. Selection bias may have occurred because participants willing to undergo lumbar puncture may not represent the broader population of individuals with cognitive concerns [16].

Clinical Implications

These findings support incorporation of CSF biomarker testing into diagnostic workflows for patients presenting with cognitive decline, particularly when clinical assessment alone cannot distinguish AD from other etiologies. The combined panel's high sensitivity at the MCI stage suggests a role in identifying individuals at highest risk for progression, enabling earlier initiation of emerging disease-modifying therapies and more targeted enrollment in clinical trials. Clinicians should interpret biomarker results within the complete clinical context, as no single test can replace thorough neurological, neuropsychological, and neuroimaging evaluation [17].

Conclusions

This research demonstrated that a combined CSF biomarker panel comprising total tau, phosphorylated tau at threonine 181, and amyloid-beta 42 achieves excellent diagnostic accuracy for Alzheimer's disease detection and good discriminative performance against non-AD dementias. The panel's sensitivity of 94.3% and specificity of 91.7% for distinguishing AD from cognitively normal individuals, combined with 91.0% detection accuracy at the MCI stage, supports its clinical utility for early diagnosis. Biomarker trajectories across disease stages followed the predicted cascade of declining amyloid with rising tau markers,

confirming their biological validity as disease indicators. Implementation of standardized CSF biomarker testing in memory clinic settings could improve diagnostic precision, facilitate earlier therapeutic intervention, and enable more efficient participant selection for clinical trials evaluating disease-modifying treatments. Validation in larger multicenter cohorts and direct comparison with emerging blood-based biomarker platforms represent necessary next steps.

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Contributions Not Qualifying for Authorship

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