

Review Article

Cerebrospinal Fluid Biomarkers in the Differential Diagnosis of Normal Pressure Hydrocephalus

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Abstract

Background: Idiopathic normal pressure hydrocephalus (iNPH) is a treatable cause of gait disturbance, cognitive impairment and urinary incontinence in older adults, but overlaps clinically with Alzheimer's disease (AD).

Objective: To review evidence on cerebrospinal fluid (CSF) biomarkers used to differentiate iNPH from AD and predict shunt-responsiveness.

Methods: Narrative review of diagnostic-criteria papers, biopsy-correlation studies, biomarker case-control series, meta-analyses and shunt-outcome cohorts.

Findings: iNPH shows low amyloid- β 42 with normal or modestly elevated tau/phospho-tau, contrasting with the low amyloid- β 42/high tau pattern of AD; phospho-tau distinguishes the two with high sensitivity and specificity. Leucine-rich alpha-2-glycoprotein, neurofilament light chain and L1CAM add value. CSF tap testing retains higher specificity than any single biomarker for predicting shunt response.

Conclusions: No single CSF biomarker substitutes for dynamic CSF testing, but biomarker panels usefully flag comorbid neurodegeneration and refine patient counselling.

Keywords: Normal pressure hydrocephalus; Cerebrospinal fluid biomarkers; Amyloid-beta; Tau protein; Shunt responsiveness

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Introduction

Idiopathic normal pressure hydrocephalus (iNPH) is a communicating hydrocephalus of older adults presenting with the classic Hakim triad of gait disturbance, cognitive impairment and urinary incontinence, occurring with normal opening pressure and ventriculomegaly out of proportion to cortical atrophy [1]. It is among the few potentially reversible causes of dementia-like presentations, with cerebrospinal fluid (CSF) shunting producing meaningful improvement in a substantial proportion of well-selected patients, as confirmed most recently by a placebo-controlled randomized trial [2].

International and Japanese guidelines have refined diagnostic criteria and incorporated imaging findings such as disproportionately enlarged subarachnoid-space hydrocephalus (DESH) into structured algorithms [3,4].

Despite this progress, patient selection remains difficult. The clinical triad is nonspecific in the elderly, and Alzheimer's disease (AD) is the most important differential and the most frequent comorbidity: cortical biopsy series report AD-consistent amyloid and tau pathology in roughly one-fifth to two-thirds of iNPH patients undergoing shunt surgery [5,6,7]. Distinguishing "pure" iNPH from iNPH with comorbid AD, and from AD alone misread as hydrocephalus because of age-related ventriculomegaly, matters clinically because it shapes expectations about which symptom domains (typically gait more than cognition) are likely to improve after shunting, and because unnecessary surgery in patients whose decline is driven predominantly by neurodegeneration exposes them to procedural risk without commensurate benefit. CSF biomarkers, already validated for AD diagnosis, have therefore been investigated extensively as adjuncts for differentiating iNPH from AD and for predicting which patients will benefit from shunting. This review synthesises that literature, covering diagnostic guidelines, the core amyloid/tau panel, emerging candidate biomarkers, the relationship between biomarkers and CSF dynamic testing, and dedicated shunt-outcome studies.

Diagnostic Challenge of Overlapping Neurodegeneration

Gait disturbance, cognitive slowing and urinary symptoms are common in both iNPH and AD, and neuroimaging alone cannot reliably separate the two, particularly when ventriculomegaly and cortical atrophy coexist. Early series established that concomitant AD pathology, identified at cortical biopsy during shunt placement, is present in a meaningful minority of clinically diagnosed iNPH

patients, though its presence does not uniformly predict a worse shunt outcome when iNPH is accurately diagnosed [5]. A larger biopsy cohort of 468 patients confirmed that amyloid and tau histopathology carry independent long-term prognostic value beyond the clinical syndrome [7], and a more recent series found AD-consistent pathology in roughly 19% of 142 shunted patients, correlating biopsy findings with high-volume lumbar puncture results [6]. This overlap motivates the search for a fluid biomarker that can flag comorbid AD without requiring invasive biopsy, since misattributing AD-driven decline to reversible hydrocephalus—or vice versa—has direct consequences for surgical candidacy and prognostic counselling.

CSF Amyloid and Tau Biomarkers

The core AD CSF signature—reduced amyloid-β42 (Aβ42) with elevated total tau (t-tau) and phosphorylated tau (p-tau)—is well established. Early work in iNPH found a partially overlapping but distinguishable pattern: Aβ42 is reduced in iNPH nearly as much as in AD, but t-tau and p-tau are typically normal or only mildly elevated, contrasting with the marked tau elevation of AD [8,9]. A systematic review and meta-analysis pooling ten studies (413 iNPH, 186 AD, 147 controls) confirmed this pattern: relative to AD, p-tau achieved the best discrimination (sensitivity 94.3%, specificity 85.1%), followed by t-tau (82.8%/84.2%), while Aβ42 alone performed poorly (81.3%/50.6%) because it is low in both conditions [10]. Subsequent systematic reviews of iNPH versus AD and subcortical ischemic vascular disease reached concordant conclusions, with t-tau and p-tau—rather than Aβ42—carrying most of the discriminatory weight [11,12].

An important caveat is that hydrocephalus itself appears to suppress CSF concentrations of amyloid precursor protein fragments and tau, plausibly through compression of the interstitial space and impaired protein clearance; these levels rise after shunting decompresses

the brain, meaning a single preoperative sample may understate true neurodegeneration and complicate cross-sectional comparison with AD [13]. This "global suppression" hypothesis explains why an isolated low Aβ42—the single most consistent iNPH finding—is a poor discriminator of AD in this population despite being highly informative in patients without hydrocephalus, and argues for interpreting biomarkers as ratios (Aβ42/Aβ40, p-tau/Aβ42) rather than as absolute concentrations. Consistent with this pathophysiological account, a large biomarker cohort (the Bologna Pro-Hydro study) found iNPH patients had significantly lower Aβ42, Aβ40, t-tau and p-tau than controls, alongside elevated neurofilament light chain—an axonal-injury marker not suppressed by the same mechanism [14]. A comparison of iNPH against multiple neurodegenerative dementias similarly found higher Aβ42 and lower t-tau/p-tau in iNPH than in AD and Lewy body dementia [15]. Overall, the Aβ42/tau pattern is useful chiefly as a ratio or combination rather than through any single analyte in isolation, and clinicians should be cautious about applying standard AD cutoffs, derived in non-hydrocephalic populations, directly to iNPH CSF.

Table 1: Direction of change in key CSF biomarkers in idiopathic normal pressure hydrocephalus (iNPH) versus Alzheimer's disease (AD) and healthy controls [8,9,10,11,14,15,13,16].				
Biomarker	iNPH vs controls	AD vs controls	iNPH vs AD	Source
Amyloid-β42	Reduced	Reduced	Similar or slightly higher in iNPH	chen2017, manniche2019
Total tau (t-tau)	Normal or mildly reduced	Markedly elevated	Lower in iNPH	kapaki2007, chen2017
Phospho-tau (p-tau)	Normal or mildly reduced	Markedly elevated	Lower in iNPH; best single discriminator	chen2017, jeppsson2013
Neurofilament light	Elevated	Elevated	Elevated in both; not iNPH-specific	abururumeileh2019

Biomarker	iNPH vs controls	AD vs controls	iNPH vs AD	Source
LRG	Elevated	Not routinely elevated	Elevated relatively specifically in iNPH	nakajima2011
Aβ42/Aβ40 or p-tau/Aβ42 ratio	Abnormal	Abnormal (AD pattern)	Pattern differs; ratio more informative than Aβ42 alone	graffradford2014, said2022

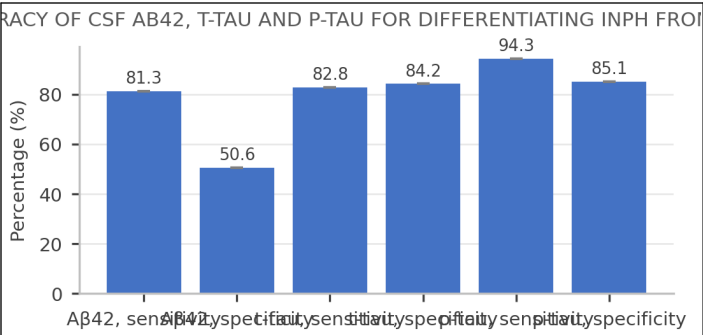


Figure 1: Pooled sensitivity and specificity of CSF amyloid-β42 (Aβ42), total tau (t-tau) and phosphorylated tau (p-tau) for differentiating iNPH from Alzheimer's disease, meta-analysis of 10 studies (413 iNPH, 186 AD) [10].

Other Candidate CSF Biomarkers

Beyond the core AD panel, several iNPH-enriched biomarkers have been proposed. Leucine-rich alpha-2-glycoprotein (LRG), discovered through CSF proteomics, is specifically elevated in iNPH; combining an LRG cutoff of 67 ng/mL with a tau cutoff of 200 pg/mL achieved 81.6% sensitivity and 78.6% specificity for shunt responsiveness in one cohort, and LRG levels were significantly higher in shunt responders than non-responders (96.8 versus 29.2 ng/mL) [16]. A follow-up study confirmed elevated CSF LRG alongside the expected reduction in AD-type biomarkers, supporting LRG's utility independent of comorbid amyloid pathology [17]. Mass-spectrometry-based proteomic panels have additionally implicated L1 cell adhesion molecule (L1CAM) and other proteins that distinguish iNPH from both controls and AD [18], and a large-scale unbiased CSF proteomic analysis has begun to define molecular signatures specific to iNPH, offering candidate biomarkers

beyond the classical panel [19].

Neurofilament light chain (NfL), a marker of axonal injury, is consistently elevated in iNPH relative to controls, though not specifically versus other neurodegenerative conditions; in a large series distinguishing iNPH from 297 non-iNPH "mimics," a combination of t-tau, Aβ40 and monocyte chemoattractant protein-1 (MCP-1)—reflecting astrocyte activation—separated iNPH from cognitive and movement-disorder mimics with good accuracy [20]. NfL also carries prognostic weight: higher preoperative NfL and t-tau were associated with less favourable outcome after shunt surgery in a cohort of 455 patients, although most patients with elevated markers still improved [21]. Collectively, these biomarkers suggest that no single analyte captures iNPH pathophysiology, but multi-marker panels combining amyloid, tau, and markers of axonal or astrocytic injury outperform any individual biomarker.

CSF Dynamic Testing (Tap Test/Lumbar Drainage) versus Biomarkers

Dynamic CSF testing remains the clinical mainstay for predicting shunt response. The high-volume lumbar tap test (removal of 30–50 mL CSF with pre/post gait and cognitive assessment) and prolonged external lumbar drainage (ELD) were validated in a prospective study of 151 patients, in which 66% improved after ELD and 84% of ELD-positive patients subsequently improved after shunting [22]. A dedicated analysis of tap-test performance across grading scales found sensitivity and specificity that varied considerably by outcome measure and threshold [23], and a formal cost-effectiveness and accuracy analysis concluded that ELD approaches but does not reach ideal sensitivity and specificity, and that no single screening test—biomarker or dynamic—is definitive on its own [24].

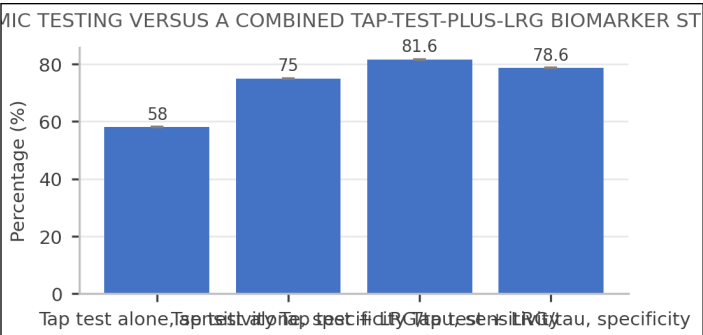


Figure 2: Predictive accuracy for shunt responsiveness of the CSF tap test alone versus a combined tap-test-plus-leucine-rich alpha-2-glycoprotein (LRG)/tau biomarker strategy [23,16].

Compared against dynamic testing, individual CSF biomarkers generally show lower specificity for shunt response, but they carry two advantages: they are obtainable from the same single lumbar puncture used diagnostically, avoiding a separate prolonged drainage admission with its associated bed-days and small risk of meningitis, and they can flag comorbid AD pathology that dynamic testing cannot detect. The complementary, rather than competing, relationship between the two approaches is illustrated by the LRG-plus-tau-test combination, in which biomarker status stratified tap-test-positive patients into four groups with markedly different rates of postoperative cognitive improvement, from 100% of shunt responders in the low-tau/high-LRG group to only 33% in the high-tau/low-LRG group [16]. This kind of stratification suggests biomarkers are best positioned as a triage or risk-refinement layer applied on top of, rather than instead of, dynamic testing.

Predicting Shunt Responsiveness

Beyond simple case-control differentiation, several studies have directly examined which CSF biomarkers predict postoperative outcome. A study of ventricular CSF found that a higher phosphorylated-tau/Aβ42 ratio correlated with cortical AD pathology at biopsy and with less favourable long-term shunt outcome, though the authors cautioned against using this ratio alone to exclude patients from surgery [25]. A systematic review and

meta-analysis of 13 studies spanning 37 unique CSF and venous biomarkers found that lumbar p-tau and t-tau were significantly higher in shunt non-responders, but that no single biomarker achieved both high sensitivity and specificity for predicting response, underscoring the continued primacy of dynamic testing [26]. A prospective cohort measuring Aβ1-40, Aβ1-42, t-tau, p-tau and NFL found that lower levels of each biomarker individually predicted better long-term gait outcome after shunting, reinforcing the concept that a "cleaner" neurodegeneration profile predicts better surgical response [27]. The 2025 PENS trial, the first placebo-controlled randomized trial of shunting in iNPH, confirmed that shunt surgery significantly improves gait and reduces falls specifically among patients selected via positive response to CSF drainage testing, reinforcing dynamic testing's centrality even as biomarker research matures [2].

Table 2: Selected studies relating CSF biomarkers or dynamic testing to shunt-responsiveness prediction in iNPH [22,16,25,26,27,2].

Study (year)	Design / n	Predictor(s) evaluated	Key finding
Marmarou 2005	Prospective, n=151	External lumbar drainage (ELD)	66% improved after ELD; 84% of ELD-positive patients improved after shunting
Nakajima 2011	n=90 (tap test); 52 shunted	Tap test + CSF LRG/tau	Combined strategy: 81.6% sensitivity, 78.6% specificity for shunt response
Patel 2012	Ventricular CSF cohort	p-tau/Aβ42 ratio	Higher ratio correlated with AD pathology at biopsy and less favourable outcome
Thavarajasingam 2022	Systematic review, 13 studies, 37 biomarkers	CSF and venous biomarkers	Lumbar p-tau and t-tau higher in non-responders; no single biomarker sufficiently accurate alone

Study (year)	Design / n	Predictor(s) evaluated	Key finding
Darrow 2022	Prospective cohort	Aβ1-40, Aβ1-42, t-tau, p-tau, NFL	Lower levels of each biomarker individually predicted better long-term gait outcome
Luciano 2025 (PENS trial)	Randomized , placebo-controlled	Response to CSF drainage testing (selection criterion)	Shunting significantly improved gait and reduced falls in drainage-responsive patients

Current Limitations and Research Directions

Substantial heterogeneity across studies—in CSF sampling site (lumbar versus ventricular), assay platform, patient selection, and outcome definitions—limits direct comparison and explains some contradictory findings, particularly for t-tau and p-tau associations with outcome [26]. The biological confound that hydrocephalus itself suppresses baseline biomarker levels, normalising partially after shunting, complicates the interpretation of any single preoperative measurement as a pure marker of neurodegeneration [13]. Emerging unbiased proteomic approaches may identify iNPH-specific signatures less confounded by coexisting AD pathology [19], while refined quantitative imaging biomarkers such as automated DESH scoring offer a complementary, non-invasive axis for multimodal prediction models that combine imaging, dynamic testing and CSF biomarkers [28]. Prospective, adequately powered studies using standardized biomarker panels and harmonized outcome measures, ideally nested within trials such as the PENS study, are needed before any CSF biomarker can be recommended as a standalone diagnostic or prognostic test.

Conclusion

CSF biomarkers meaningfully inform, but do not replace, the differential diagnosis and shunt-responsiveness prediction of iNPH. The combination of reduced Aβ42 with relatively preserved tau distinguishes iNPH from AD

with reasonable accuracy, especially using p-tau, while iNPH-enriched markers such as LRG and injury markers such as NFL add prognostic value. Dynamic CSF testing retains higher specificity for shunt response than any single biomarker, and current evidence supports using CSF biomarkers as an adjunct—for flagging comorbid neurodegeneration and refining patient counselling—rather than as a substitute for tap testing or lumbar drainage in surgical decision-making.

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