

GLYMPHATIC SYSTEM ROLE IN NPH MANAGEMENT

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INTRODUCTION

Normal pressure hydrocephalus (NPH) is a progressive neurodegenerative disorder, often underdiagnosed, characterized by **gait disturbance, cognitive decline, and urinary incontinence**. Its pathophysiology is increasingly understood as an **interstitial fluidopathy of the central nervous system**, involving dysfunction of the **glymphatic system (GS)**. The GS is responsible for cerebrospinal fluid (CSF) circulation and clearance of metabolic waste, and its impairment may contribute to neurodegeneration. **Diffusion Tensor Imaging Analysis Along the Perivascular Space (DTI-ALPS)** has emerged as a non-invasive MRI technique to estimate GS activity. This study aimed to investigate whether DTI-ALPS sequences could support diagnostic workup and prognosis in patients undergoing **tap test (TT)** and **ventriculoperitoneal shunt (VPS)**.

MATERIAL & METHODS

We prospectively enrolled **21 patients** with probable NPH according to clinical and radiological guidelines. Exclusion criteria included previous neurosurgery, other neurological diseases, and MRI contraindications.

The diagnostic pathway consisted of:

- **T0:** Baseline 3T MRI with DTI-ALPS sequences (Figure 1)
- **T1:** Clinical assessment and TT with CSF biomarker analysis (*beta-amyloid peptides, Tau protein*), followed by post-TT 3T MRI (Table 1.)
- **T2:** VPS surgery for TT-responders, with intraoperative CSF biomarkers (Table 2)
- **T3:** Three-month follow-up with MRI and neurological scales.

15 patients responded to TT and underwent VPS (R); **6** were non-responders (NR). **8** age-matched healthy controls (HC) also underwent DTI-ALPS. Clinical status was assessed with Japanese NPH Grading Score Revised (JNPHGSR), Tinetti Score, Timed Up and Go (TUG), Mini Mental Status Examination (MMSE), and Frontal Assessment Battery (FAB).

RESULTS

Baseline ALPS-index:

NPH patients had significantly lower values than HC (R: 1.003; NR: 0.960; HC: 1.263; $p < 0.01$). (Table 3)

Response to TT and VPS:

- Responders showed a significant ALPS-index increase post-TT ($p = 0.0499$) and post-VPS ($p = 0.041$). (Table 3)
- Non-responders showed no significant change. (Table 3)

Clinical outcomes:

- All responders improved after VPS, with significant gains in Tinetti, TUG, MMSE, and JNPHGSR scores at follow-up.
- Non-responders showed no clinical benefit.

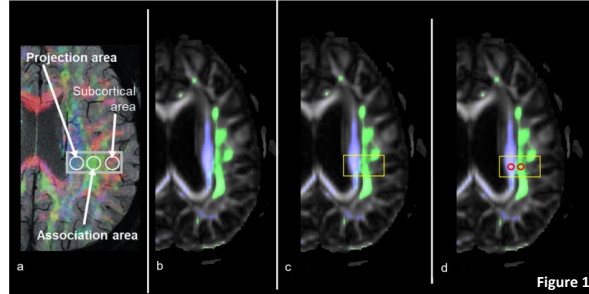
CSF biomarkers (table 2):

Tau and p-tau increased intraoperatively, then decreased at follow-up, while amyloid peptides rose at late evaluation, suggesting enhanced clearance and reduced CSF dilution.

DISCUSSION & CONCLUSIONS

Patients with NPH demonstrated significantly lower ALPS values compared with healthy controls, supporting glymphatic dysfunction as a key pathogenic mechanism. **TT-responders showed a significant increase in ALPS index, which was maintained three months after VPS, paralleling clinical improvement.** Non-responders exhibited no change. Clinical predictors of responsiveness included younger age, lower baseline JNPHGSR, and relatively preserved cognition. Traditional radiological markers such as Evans Index and callosal angle did not correlate with ALPS. **CSF biomarkers showed a pattern of reduced amyloid proteins and low-normal tau levels, with postoperative increases likely reflecting improved clearance.**

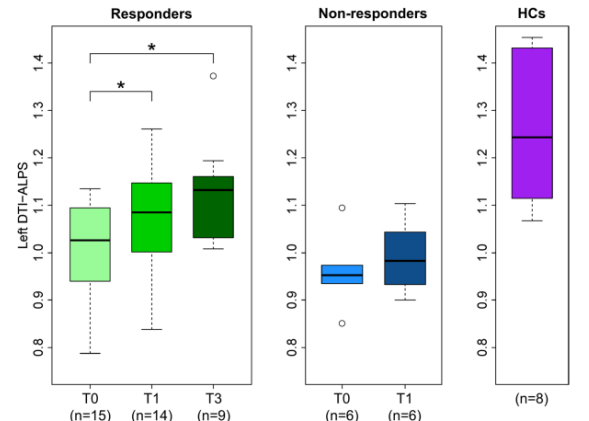
DTI-ALPS appears to be a promising indirect marker of glymphatic activity in NPH, reflecting both disease severity and treatment response. Still, validation in larger, standardized cohorts is required. **Integrating GS assessment into routine practice could refine diagnosis, improve prognostic accuracy, and enhance therapeutic decision-making in NPH.**



	Enrolled patients (total)		TT-Responders		TT-Non-responders		
	Median	IQR	Median	IQR	Median	IQR	p-value
Number of patients	21		15		6		
Males (%)	15 (71%)		10 (67%)		5 (83%)		
Females (%)	6 (29%)		5 (33%)		1 (17%)		
Clinical parameters							
Age (years)	78	75–81	77	75–80	80.5	79–82	0.03*
JNPHGSR (t, pre-TT)	6	4–7	5	4–7	7	7–8	0.01*
MMSE (t ₀)	26	20–29	28	22–30	20.5	20–24	0.08
Tinetti score (t, pre-TT)	17	15–21	18	15–22.5	14	10–15	0.02*
Tinetti score (t, post-TT)	22	18–24	22	18–24	14	10–17	0.002*
FAB (t ₀)	12	9–15	14	12–16	9.5	8–12	0.08
TUG (s) (t, pre-TT)	24.5	19.5–29.5	22.5	19–27	28.5	26–30	0.22
TUG (s) (t, post-TT)	19.5	16–24.5	18	15–20	26	25–27	0.007*
Radiological characteristics (t₀)							
Evans Index	0.35	0.33–0.37	0.33	0.33–0.37	0.37	0.35–0.4	0.14
NPH Radscale	8	7–9	8	7–9	7.5	6–9	0.69
Transcallosal angle (°)	80	65–85	80	74–85	82.5	65–90	0.69
CSF Biomarkers characteristics (t₀)							
Tau protein (pg/ml)	223	159–316	200	150–285	306	207–431	0.11
p-tau (pg/ml)	28.5	21.1–42.2	26.6	20.7–40.6	34.7	26.5–51.4	0.24
Aβ ₄₂ (pg/ml)	496	427–753	463	423–755	620	494–750	0.38
Aβ ₄₀ (pg/ml)	6672	4696–8089	6392.5	4158–8131	7086	5345–7645	0.40
Aβ ₄₂ /Aβ ₄₀ ratio	0.10	0.07–0.11	0.101	0.07–0.105	0.096	0.07–0.11	0.93

Clinical Outcomes	Tap Test		VPS		p-value	3 months post-VPS		p-value
	Median	IQR	Median	IQR		Median	IQR	
n = 15			n = 15			n = 10		
Total Tau (pg/ml)	200	150–285	1278	851–2000	0.01*	455	258–614	0.02*
p-tau (pg/ml)	26.6	20.7–40.6	88.5	60.5–239	0.01*	59.7	33–79	0.01*
Aβ ₄₂ (pg/ml)	463	423–755	475	382–588	0.06	730	439–1232	0.06
Aβ ₄₀ (pg/ml)	6392.5	4158–8131	4955	4014–5918	0.04*	9294	6424–11,876	0.04*
Aβ ₄₂ /Aβ ₄₀	0.101	0.07–0.105	0.1	0.1–0.1	0.7	0.09	0.09–0.1	0.3

Time	Left DTI-ALPS index, mean (SD)		
	Responder	Non-responder	HC
T0 – baseline	1.003 (0.108) [†]	0.960 (0.079) [‡]	1.263 (0.161)
T1 – post-TT	1.069 (0.122)	0.991 (0.078)	NA
T3 – post-VPS	1.120 (0.117)	NA	NA



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