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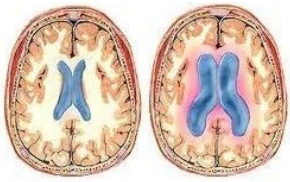

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CSF Biomarkers of Alzheimer's Disease and Response to Ventriculo-Peritoneal Shunting in Normal Pressure Hydrocephalus

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Introductions

- **CSF biomarker profiling is essential to distinguish idiopathic normal pressure hydrocephalus (iNPH) from Alzheimer's disease (AD).**
- **In AD, the profile is characterized by markedly reduced Aβ42, decreased Aβ42/Aβ40 ratio, and elevated t-tau and p-tau levels.**
- **iNPH exhibits a distinct pattern due to periventricular hypometabolism of Aβ [1] and impaired glymphatic clearance [2].**
- **Aβ42 is mildly reduced versus controls but higher than in AD; t-tau and p-tau show slight elevation, and Aβ42/Aβ40 ratio is largely preserved [3,4].**
- **Among biomarkers, p-tau provides the highest discriminatory power between iNPH and AD, reflecting divergent pathophysiology [5].**
- **iNPH patients with an AD-like CSF profile tend to have poorer shunt outcomes, underscoring its prognostic value [6].**

Materials and Methods

- We enrolled **80 iNPH patients** (2019–2024, Careggi, Florence) diagnosed as *possible iNPH* (2021 Japanese guidelines).
- **Exclusion criteria**: TBI, SAH, brain tumors, other neurological disorders.
- **Each patient underwent:** Clinical and Neuropsychological assessment, MRI/CT, and **TAP-test (30 ml CSF).**

1. **Motor tests** included SPPB, stand-up, 10-m walk, and finger tapping.
2. **Cognitive tests** included MMSE, MoCA, FAB, TMT-A/B, verbal fluency, SDMT, all assessed before TAP-test, at 6 h and 24 h.
3. **CSF biomarkers measured**: Aβ1–42, Aβ1–42/40, t-tau, p-tau181 and ratios.

- **VP shunt surgery** was performed in **26 patients; 15 patients** were followed up (mean 1.6 yrs) with the same assessments.

Aim of the study

Identifying preoperative motor, cognitive, demographic, and CSF biomarkers in iNPH patients that could predict a favorable response to VP shunting.

Results

- Patients (n=80, mean age 75 years) predominantly presented with gait disturbance (72.5%) and the complete clinical triad (71.3%). Following the TAP-test, 70–75% improved cognitively and 37% motorically, with no baseline differences between shunted and non-shunted groups.
- Operated patients showed significantly higher values of **ΔFVF (p = 0.013), SPPB at 6 h (p = 0.012) and at 24 h (p = 0.004), ΔSPPB (p = 0.012), and mean gait speed at 24 h (p = 0.021)** compared to non-operated patients.
- Patients reporting subjective cognitive improvement had a **younger age at symptom onset (p = 0.012) and significantly lower CSF t-tau and p-tau levels (t-tau: p = 0.020; p-tau: p = 0.028).**
- **Lower CSF t-tau and p-tau concentrations** were also significantly associated with a higher frequency of subjective urinary symptom improvement **(t-tau: p = 0.015; p-tau: p = 0.009).**
- **Higher CSF p-tau levels** were **inversely** associated with **postoperative cognitive improvement (B = –0.412, OR = 0.66, p = 0.046). ROC analysis** showed excellent predictive **accuracy** in this model **(AUC = 0.969; 90% accuracy, 87.5% sensitivity, 91.7% specificity).**

Variable	non-DVP	DVP	p
ΔFVF	-2.15 ± 11.23	3.27 ± 6.09	**0.013***
SPPB 6h	4.10 ± 3.49	6.67 ± 3.69	**0.012***
SPPB 24h	4.17 ± 3.63	7.14 ± 3.72	**0.004***
ΔSPPB	-0.02 ± 2.01	1.14 ± 1.96	**0.012***
Speed 24h	0.53 ± 0.40	0.85 ± 0.59	**0.021***

Table 1: Comparison of cognitive and motor tests performed before and after the TAP-test between operated and non-operated patient groups using the Mann–Whitney U test.

Variable	Not improved	Improved	p
t-tau (Urin)	355,40 ± 235,33	191,13 ± 63,06	**0,015***
p-tau (Urin)	59,55 ± 49,99	25,38 ± 8,98	**0,009***
Age at onset (Cog)	72,93 ± 5,13	65,60 ± 7,81	**0,012***
t-tau (Cog)	310,20 ± 205,28	176,80 ± 46,28	**0,020***
p-tau (Cog)	49,18 ± 43,27	23,87 ± 7,72	**0,028***

Table 2: Comparison of descriptive variables between patients with and without urinary and cognitive improvement after VP shunt using the Mann–Whitney U test.

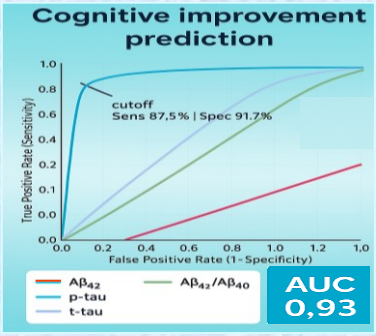

Figure1: ROC curves for p-tau, t-tau, Aβ42/Aβ40 , Aβ42 values

Discussion

1. The TAP-test confirmed its reliability as a predictor of surgical response in "possible" iNPH, showing cognitive and motor improvements consistent with previous studies **[7], [8].** Motor performance (SPPB, gait speed) and phonemic fluency were predictive of surgical selection, the latter confirming its role as a marker of executive dysfunction **[9].**
2. CSF analysis revealed that higher t-tau and p-tau levels correlated with worse prognosis and reduced improvement in cognition and urinary control. Notably, p-tau emerged as an independent and accurate negative prognostic factor **[10].**
3. Conversely, Aβ1–42 and Aβ1–42/Aβ1–40 lacked predictive value. Overall, tau pathology, rather than amyloid pathology, appears to compromise surgical efficacy, supporting CSF p-tau as a key prognostic biomarker.

Conclusions

Our study confirms that motor improvement at the TAP-test, particularly gait speed, reliably predicts surgical outcome in iNPH. Elevated CSF p-tau correlates with poor response, whereas amyloid markers show limited prognostic value.
Patients with predominant motor symptoms and negative AD biomarkers appear the best surgical candidates, supporting CSF biomarker integration to optimize patient selection and outcomes.

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