Aquaporin-4 cerebrospinal fluid levels are higher in Idiopathic Normal Pressure Hydrocephalus

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BACKGROUND

Altered cerebrospinal fluid (CSF) dynamics have increasingly been recognized as a key pathophysiological mechanism in idiopathic normal pressure hydrocephalus (iNPH). Aquaporin-4 (AQP4), a water channel protein highly expressed in the central nervous system particularly in the perivascular endfeet of astrocytes surrounding blood vessels, plays a critical role in the glymphatic system (1). This system facilitates the exchange between CSF and interstitial fluid, supporting the clearance of metabolic waste from the brain.

Previous studies investigating CSF AQP4 levels in iNPH have reported reduced concentrations or values below the limit of detection (2).

This study aims to quantify CSF AQP4 levels in iNPH patients and cognitively healthy controls, and to examine their relationship with established CSF biomarkers of neurodegeneration.

METHODS

- ✓ Fifty-seven participants were recruited at the Dementia Center, University of Torino:
  - 30 patients diagnosed with probable iNPH, according to current diagnostic criteria;
  - 27 age-matched cognitively healthy controls.
- ✓ All participants underwent lumbar puncture. CSF samples were collected in polypropylene tubes, centrifuged at 1500xg for 10 minutes, aliquoted, and stored at -80°C until analysis.
- ✓ AQP4 concentrations were measured using a commercially available ELISA kit (Cloud-Clone Corp).
- ✓ Core CSF biomarkers of neurodegeneration Aβ42, Aβ42/40 ratio, total tau (t-Tau), and phosphorylated tau at threonine 181 (p-Tau181) were quantified using the Lumipulse platform (Fujirebio, Ghent, Belgium).

RESULTS

- ✓ CSF AQP4 levels were significantly higher in iNPH patients compared to controls (1317.1± 534.96 pg/mL vs 823.8± 473.38 pg/mL; p= 0.002), and this difference remained significant after adjusting for age (Fig. 1).
- ✓ Within the iNPH group, a significant negative correlation was observed between AQP4 and the Aβ42/40 ratio (r= -0.50, p= 0.010), (Fig. 2).
- ✓ No significant correlations were found with Aβ42, t-Tau, or p-Tau181 levels.

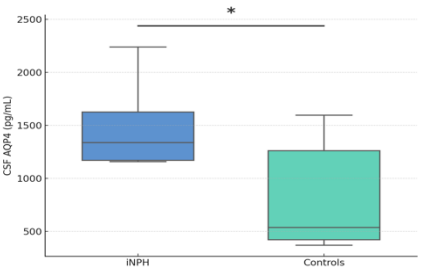

Fig. 1. Boxplots illustrate differences in CSF AQP4 levels between iNPH and controls.

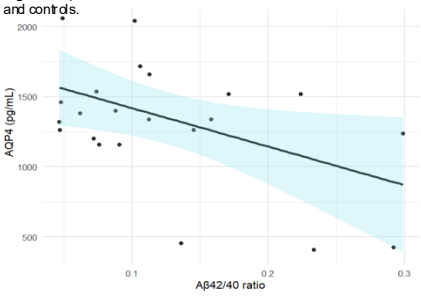

Fig. 2. Correlation between AQP4 levels and Aβ42/40 in iNPH.

CONCLUSION

These findings indicate elevated CSF AQP4 levels in iNPH patients, supporting the hypothesis that impaired water transport and glymphatic dysfunction may contribute to the disease. Similar increases in CSF AQP4 have also been reported in patients with Alzheimer's disease (3).

In our study, we also identified a significant negative correlation between CSF AQP4 levels and the Aβ42/40 ratio, indicating a potential link between glymphatic clearance and amyloid metabolism. Finally, AQP4 could represent a promising potential biomarker for iNPH. Further studies in larger populations are needed to confirm our findings.

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