



LEADING TOPIC

Leading Topic Editor: Olga P. Fermo, MD, Department of Neurology, Mayo Clinic, Jacksonville, Florida, United States

Neuronal pentraxin 2 correlates with neurodegeneration but not cognition in idiopathic normal pressure hydrocephalus (iNPH)

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ABSTRACT

Aim of study. Neuronal pentraxin-2 (NPTX2) is a synaptic protein responsible for modulating plasticity at excitatory synapses. While the role of NPTX2 as a novel synaptic biomarker in cognitive disorders has been elucidated recently, its role in idiopathic normal pressure hydrocephalus (iNPH) is not yet understood.

Clinical rationale for study. To determine if NPTX2 predicts cognition in patients with iNPH, and whether it could serve as a predictive marker for shunt outcomes.

Materials and methods. 354 iNPH patients underwent cerebrospinal fluid drainage (CSF) as part of the tap test or extended lumbar drainage. Demographic and clinical measures including age, Evans Index (EI), Montreal Cognitive Assessment (MoCA) score, Functional Activities Questionnaire (FAQ) score, and baseline and post-shunt surgery Timed Up and Go (TUG) test scores were ascertained. CSF NPTX2 concentrations were measured using an ELISA. CSF β -amyloid 1–40 ($A\beta$ 1–40), β -amyloid 1–42 ($A\beta$ 1–42), and phosphorylated tau-181 (pTau-181) were measured by chemiluminescent assays. Spearman's correlation was used to determine the correlation between CSF NPTX2 concentrations and age, EI, MoCA and FAQ, TUG, $A\beta$ 1–40/ $A\beta$ 1–42 ratio, and pTau-181 concentrations. Logistic regression was used to determine if CSF NPTX2 values were a predictor of short-term improvement post-CSF drainage or long-term improvement post-shunt surgery.

Results. There were 225 males and 129 females with a mean age of 77.7 years (\pm 7.06). Average CSF NPTX2 level in all iNPH patients was 559.97 pg/mL (\pm 432.87). CSF NPTX2 level in those selected for shunt surgery was 505.61 pg/mL (\pm 322.38). NPTX2 showed modest correlations with pTau-181 ($r = 0.44$, $p < 0.001$) with a trend for $A\beta$ 42/ $A\beta$ 40 ratio ($r = -0.1$, $p = 0.053$). NPTX2 concentrations did not correlate with age ($r = -0.012$, $p = 0.83$) or MoCA score ($r = 0.001$, $p = 0.87$), but correlated negatively with FAQ ($r = -0.15$, $p = 0.019$).

Conclusions. While CSF NPTX2 values correlate with neurodegeneration, they do not correlate with cognitive or functional measures in iNPH. CSF NPTX2 cannot serve as a predictor of either short-term or long-term improvement after CSF drainage.

Clinical implications. These results suggest that synaptic degeneration is not a core feature of iNPH pathophysiology.

Keywords: neuronal pentraxin 2, normal pressure hydrocephalus, cerebro spinal fluid, biomarkers

(*Neurol Neurochir Pol* 2024; 58 (1): 47–53)

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Received: 13.11.2023 Accepted: 05.02.2024 Early publication date: 23.02.2024

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Introduction

Neuronal pentraxin 2 (NPTX2) is a member of the long pentraxin subfamily, a group of evolutionarily conserved proteins that play a role in regulating various processes in the brain and periphery [1]. NPTX2 has been implicated in glutamatergic signalling, which is involved in synaptic transmission and plasticity [1]. Disruptions in glutamatergic signalling have been recognised in various neurological disorders, including mild cognitive impairment (MCI) and Alzheimer's Disease (AD) [2]. Furthermore, NPTX2 plays a role in the formation and maturation of excitatory synapses [1]. In cerebrospinal fluid (CSF), reduced levels of NPTX2 have been observed in AD [3], genetic frontotemporal dementia [4], and dementia with Lewy bodies [5], leading to its promising potential use as a biomarker in these disorders.

Idiopathic normal pressure hydrocephalus (iNPH) is a neurological disorder that typically manifests with a triad of symptoms consisting of gait disturbance, cognitive dysfunction, and urinary incontinence [6]. Surgical insertion of a shunt, a common form of treatment in iNPH, is associated with a high rate of adverse events including risk of infection, shunt malfunction and subsequent revision surgery, and subdural haematomas and hygromas [7, 8]. Determining better biomarkers for predicting shunt responsiveness could potentially result in having to subject fewer patients to the risk of shunt surgery. In the context of cognitive dysfunction in iNPH, disruptions in synaptic function and loss of neurons have been reported [9], but the potential mechanisms remain to be elucidated.

In the present study, we aimed to determine if NPTX2 could function as a marker of cognitive dysfunction in iNPH. Secondly, we evaluated whether CSF NPTX2 concentrations can serve as a predictor of short-term improvement after CSF drainage or long-term improvement after shunt surgery in a large iNPH cohort.

Clinical rationale for study

Identifying relevant proteins that contribute to the cognitive decline seen in iNPH may help both in identifying and in treating this condition, as well as in understanding the underlying mechanisms. NPTX2 is a proven biomarker of synaptic integrity, although it is not known whether it can serve as a marker for the cognitive dysfunction seen in iNPH. Cognitive impairment in iNPH has been hypothesised to be due to subcortical dysfunction due to poor bloodflow to these regions [10], impaired axonal signalling [11], and potentially to the impaired clearance of waste products due to glymphatic dysfunction [12].

Determining the correlation between CSF NPTX2 concentration and cognition, other CSF biomarkers, and gait function, in addition to determining whether NPTX2 concentrations could serve as a predictor of short-term improvement after CSF drainage or long-term improvement after shunt surgery,

would further help in understanding the mechanisms of cognitive impairment in NPH, and potentially serve as a predictive biomarker after shunt surgery.

Materials and methods

Research subjects

CSF was collected from 354 probable iNPH patients who had been referred to the Johns Hopkins Centre for CSF Disorders and who underwent an outpatient tap test (TT) procedure where 40 mLs of CSF was removed or a three-day external lumbar drainage (ELD) where 300 mLs of CSF was removed. All participants referred for a TT or an ELD had to meet the criteria of presenting with some degree of gait impairment and cognitive impairment, in addition to the presence of ventriculomegaly determined through neuroimaging. Patients provided written informed consent for biospecimen banking for research under a Johns Hopkins IRB-approved protocol (IRB Application Number: NA_00029413).

Gait, cognitive, and MRI assessments

All patients who underwent a TT or an ELD participated in a full battery of gait testing, both before and after CSF drainage. The Timed Up-and-Go (TUG) test was used to assess gait speed and dynamic balance. The results of the pre-procedure and post-procedure gait testing were compared and used to determine gait improvement post-CSF drainage. An improvement of 30% or greater on the TUG test was used to define responders to CSF drainage, and subsequently used to select patients for shunt surgery. Baseline cognitive function was assessed using the Montreal Cognitive Assessment (MoCA). Ability to conduct activities of daily living (ADLs) was assessed using the Functional Activities Questionnaire (FAQ). All patients also underwent a structural MRI scan of the brain to determine the presence of ventriculomegaly, defined by an Evans Index (EI) greater than 0.3.

CSF sample processing protocol

CSF was collected directly in 10 mL polypropylene tubes (Sarstedt: 62.610.018) during the TT and ELD procedures. CSF was transported at room temperature until centrifugation at 2,000 g for 15 minutes at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$. CSF was transferred from original tubes to sterile 50 mL tubes (Sarstedt: 62.547.100) and centrifuged again at the same settings as the previous spin. Samples were then separated into 500 μL aliquots in low-binding polypropylene cryovials (Sarstedt: 101093-760) within one hour of collection and stored at -80°C until thawed for biomarker analysis.

Laboratory assays

CSF A β 1–42, A β 1–40, and pTau-181 concentrations were measured using LUMIPULSE G1200 chemiluminescent ELISA (Fujirebio, Malvern, PA, USA) directly from the cryovials without sample transfer. An internal CSF control was run on each day

Table 1. Patient baseline characteristics compared by cohort (non-shunted and shunted patients)

Characteristics	Non-shunted patients (n = 245)	Shunted patients (n = 109)
Age, years mean (\pm SD)	77.9 (\pm 7.4)	77.2 (\pm 6.4)
Male sex, n (%)	153 (62.4%)	72 (65.5%)
Race, n (%)		
Caucasian	225 (91.8%)	105 (96.3%)
African American	15 (6.12%)	2 (1.81%)
Other	5 (2.04%)	2 (1.81%)
Living status, deceased, n (%)	13 (5.30%)	5 (4.58%)
MRI Evans Index (0-1), mean (\pm SD)	0.36 (\pm 0.05)	0.38 (\pm 0.04)***
Baseline MoCA score, mean (\pm SD)	21.4 (\pm 5.56)	21.2 (\pm 5.73)
FAQ score, mean (\pm SD)	10.85 (\pm 9.02)	9.68 (\pm 8.37)
Baseline TUG score, mean (\pm SD)	20.06 (\pm 25.22)	29.70 (\pm 36.59)*
Post-shunt TUG score, mean (\pm SD)		17.69 (\pm 19.56)**
NPTX2 concentration, mean (\pm SD)	584.16 (\pm 472.41)	505.61 (\pm 322.38)
pTau-181 concentration, mean (\pm SD)	35.91 (\pm 27.25)	29.78 (\pm 20.34)*
A β 40 concentration, mean (\pm SD)	7,761.34 (\pm 3,158.35)	6,994.87 (\pm 2,964.27)*
A β 42 concentration, mean (\pm SD)	865.69 (\pm 385.77)	816.48 (\pm 366.64)
A β 42/A β 40 ratio, mean (\pm SD)	0.110 (\pm 0.03)	0.119 (\pm 0.03)**
NFL concentration, mean (\pm SD)	2,156.40 (\pm 1,679.10)	2,062.12 (\pm 1,832.94)
Aqueductal stenosis, n (%)	10 (4%)	5 (4.5%)
DESH, n (%)	71 (29%)	57 (52%)***
Cerebral atrophy, n (%)	46 (19%)	20(18%)
White matter disease, n (%)	137 (56%)	57 (52%)
Lacunar stroke, n (%)	25 (11%)	14 (13%)
Large vessel stroke, n (%)	10 (4%)	5 (4.5%)

Patients who were unable to complete the TUG were assigned a baseline TUG score of 300. Shunted patients who were unable to complete the TUG were assigned a post-shunt TUG score of 300. Additionally, 15 patients were not available for post-shunt surgery gait testing, so measures were not collected from these patients and they were also excluded. 97 patients who did not complete the FAQ were assigned a score of 999. A β 40 — β -amyloid 40; A β 42 — β -amyloid 42; DESH — disproportionately enlarged subarachnoid space hydrocephalus; FAQ — Functional Activities Questionnaire; MoCA — Montreal Cognitive Assessment; NPTX2 — neuronal pentraxin 2; pTau-181 — phosphorylated tau 181; TUG — Timed Up-and-Go; *p < 0.05, **p < 0.01, ***p < 0.001

that samples were analysed. NPTX2 concentration was measured by an in-house ELISA assay as previously described [13]

Statistical analysis

CSF NPTX2 concentrations were compared against baseline characteristics including age, MoCA score, FAQ score, baseline TUG score, post-shunt TUG score, Evans Index, A β 1–42/1–40 ratio, and pTau-181 concentration. Spearman correlations were used to determine the correlation between CSF NPTX2 and the measures listed above. P-values of less than or equal to 0.05 were considered statistically significant. To determine if NPTX2 concentrations were a predictor of short-term improvement, defined as one hour after TT or ELD, or long-term improvement defined as two years median post-shunt surgery, simple univariate logistic regression models were used. Ten-fold cross-validation was used to evaluate the logistic regression models, and the means of the area under

the receiver operating curve (AUC) values were calculated and plotted to compare model performance. The cross-validated AUC R package was used to compute 95% CIs for the cross-validated AUC estimates.

Results

The demographic characteristics of the patients included in this cohort are set out in Table 1. A total of 354 patients were included in this study, with a mean age of 77.7 years (\pm 7.06) and the majority were male (n = 225). Of these 354 patients, 109 were selected for shunt surgery and were followed for a median duration of 12 months. The MRI Evans Index was higher in the shunted group vs. the non-shunted group (0.038 \pm 0.04 vs. 0.036 \pm 0.05, p < 0.001, Tab. 1). A higher proportion of patients selected for shunt surgery had features

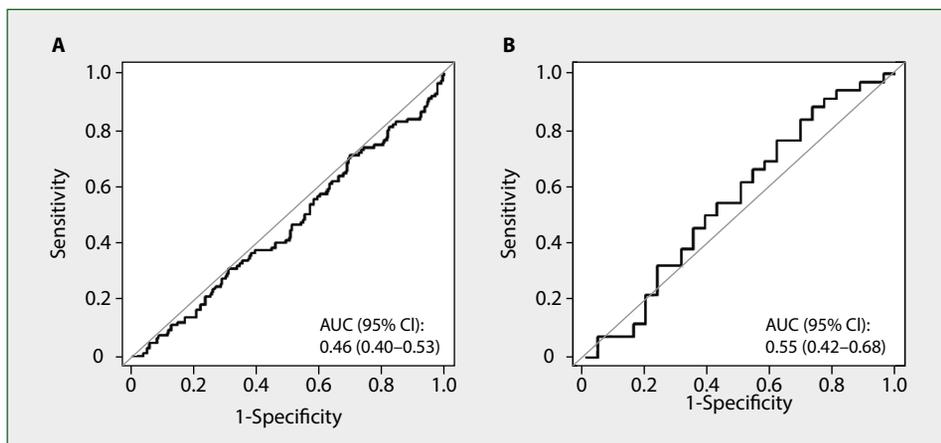


Figure 1. A. ROC for prediction of response to TT by CSF NPTX2 concentration; **B.** ROC for prediction of response to shunt by CSF NPTX2 concentration

of DESH (disproportionately enlarged subarachnoid space hydrocephalus) (52% vs. 29%, $p < 0.001$, Table 1). The groups did not differ in terms of white matter disease, cerebral atrophy, lacunar or large vessel strokes or aqueductal stenosis. CSF NPTX2 concentrations did not differ between the two groups. CSF ptau181, CSF A β 40 concentrations were lower, while the A β 42/A β 40 ratio was higher, in the shunted group (Tab. 1).

A univariate logistic regression model indicated that CSF NPTX2 concentrations were not significantly correlated with short-term improvement, defined as a 30% or greater improvement on completion of the TUG test, after TT or ELD (OR 0.80, 95% CI 0.60–1.03, p -value = 0.109) (Fig. 1). The univariate logistic regression model also indicated that CSF NPTX2 concentrations were not significantly associated with long-term improvement following shunt surgery (OR 1.08, 95% CI 0.61–2.00, p -value = 0.797) (Fig. 1).

A significant positive correlation was found between CSF NPTX2 and CSF pTau-181 concentrations ($R = 0.43$, p -value = $< 2.2 \times 10^{-16}$) (Fig. 2). In addition, significant though weak negative correlations were found between CSF NPTX2 and baseline TUG performance ($r = -0.16$, $p = 0.0025$) (Fig. 2) and between CSF NPTX2 and FAQ scores ($r = -0.15$, $p = 0.019$) (Suppl. Fig. 3), with a similar trend with A β 42/A β 40 ratio ($r = -0.1$, $p = 0.053$) (Fig. 2). There were no significant correlations found between CSF NPTX2 concentrations and age ($r = 0.008$, $p = 0.88$) (Suppl. Fig. 4), EI ($r = -0.068$, $p = 0.20$) (Suppl. Fig. 5), baseline MoCA score ($r = -0.023$, $p = 0.67$) (Fig. 2), or post-shunt surgery TUG performance ($r = -0.14$, $p = 0.17$) (Suppl. Fig. 6).

Discussion

While cognitive dysfunction is a prominent symptom of iNPH, the underlying biology is still not fully understood.

There have been several potential mechanisms proposed to explain this decline in iNPH. A study investigating the altered glymphatic system in iNPH suggested impaired waste clearance may contribute to cognitive dysfunction [14]. Another study found that proteins involved in synaptic signalling were statistically lower in iNPH, and suggested dysregulated sphingolipids that are involved in cell signalling and membrane structure could contribute to the cognitive dysfunction seen in iNPH [15]. In a post mortem study conducted by Leinonen et al. on presumed iNPH patients, it was found that vascular pathology could explain cognitive dysfunction, although specific markers of synaptic loss were not investigated [16].

Our study aimed to determine if there is a link between NPTX2, a synaptic protein shown to be affected in other neurodegenerative disorders, and cognitive decline in iNPH.

The MoCA test is a widely used and well-validated method of evaluating cognitive function and change in clinical settings as well as in NPH [17]. However, studies have explored the presence of neurological co-morbidities, particularly AD, in iNPH patients [18]. The presence of AD pathology may contribute to the cognitive impairment observed in iNPH patients. Our study showed no significant correlation between CSF NPTX2 concentration and baseline MoCA score. The FAQ provides a standardised assessment of instrumental ADL. Impairment of ADLs is a significant concern in iNPH patients due to the combination of gait and cognitive impairment. Falls, and the fear of falling, are common in the iNPH population and can further impact upon their ability to perform ADL [19].

We observed a significant, though weak, negative correlation between NPTX2 and FAQ scores.

There have been many studies that have examined CSF biomarkers in iNPH, most notably the established AD CSF biomarkers including A β 1–42, A β 1–40, pTau-181 and NFL

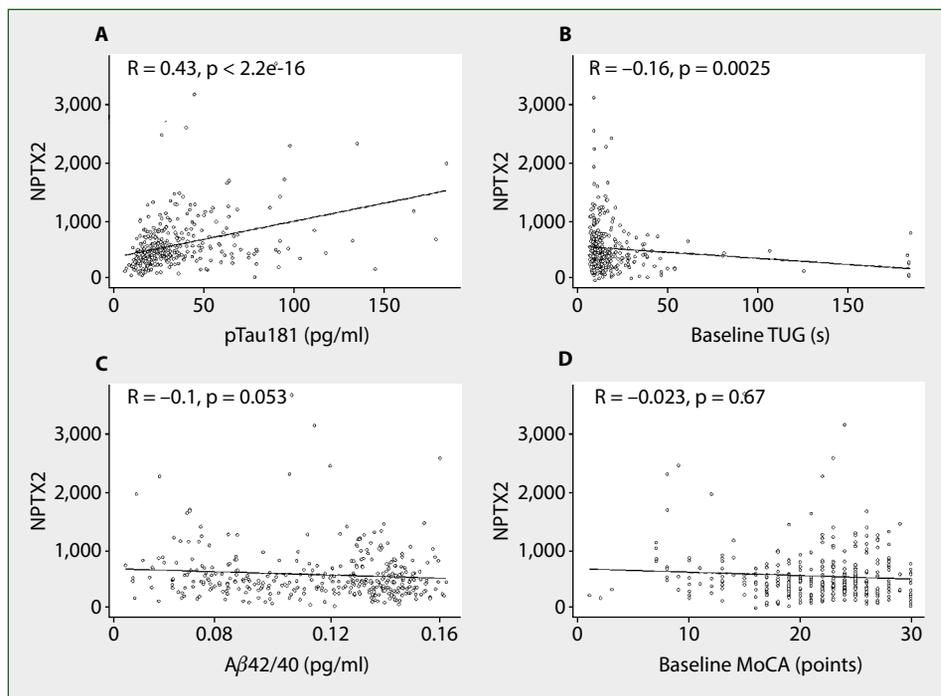


Figure 2. **A.** Correlation between CSF NPTX2 concentration and CSF pTau-181 concentration; **B.** Correlation between CSF NPTX2 concentration and baseline TUG score; **C.** Correlation between CSF NPTX2 concentration and CSF A β 42/A β 40 ratio; **D.** Correlation between CSF NPTX2 concentration and baseline MoCA score

[20,21]. Studies have focused on the measurement of CSF pTau-181 concentration primarily as a potential biomarker for differentiating NPH from other neurodegenerative diseases, including AD [22]. In the context of AD, there is an accumulation of hyperphosphorylated tau proteins, leading to increased CSF pTau-181 concentration [23]. However, the relevance of CSF pTau-181 concentration specifically in iNPH is still being investigated. Some studies have suggested that CSF pTau-181 concentration may be lower in iNPH patients compared to AD patients [23]. Our study demonstrated a significant positive correlation between CSF NPTX2 values and CSF pTau-181 values. This replicates the observation made in an earlier study, where increased CSF NPTX2 levels correlated with increased CSF pTau-181 levels to a similar extent [24].

A β s are physiological peptides that are present in normal, healthy brains and are thought to be cleared from the interstitial space of the brain across the blood-brain barrier through CSF [25]. Disruptions to the clearance of A β proteins can cause the accumulation and deposition of A β proteins, creating A β plaques [26]. Alterations in A β clearance pathways, such as the glymphatic system, have been implicated in the pathophysiology of iNPH [27]. Since iNPH causes a reduction in CSF outflow absorption, A β deposition and subsequent neurodegeneration may occur [26]. Since A β 1-40 and A β 1-42 are core CSF biomarkers of neurodegeneration, these proteins have been extensively reported in iNPH biomarker studies. A β 1-40 and A β 1-42 differ in just two amino acids. However,

they vary in metabolism, physiological function, toxicity, and aggregation mechanisms [28].

One review study showed that A β 1-42 had a prognostic value for iNPH, whereas A β 1-40 was not found to be a significant predictor [21]. However, the use of CSF AD biomarkers can be misleading when applied in the context of iNPH, as these proteins may have decreased movement from the interstitial compartment of the brain or the presence of dilution effects, where the excess CSF in iNPH dilutes the physiological components of CSF [23]. In AD, there is a characteristic imbalance in the production and clearance of A β peptides, leading to a decreased A β 42/A β 40 ratio [22]. This ratio is a well-accepted biomarker for AD, as it reflects the aggregation and deposition of A β 1-42 as amyloid plaques [29].

In our study, we found a weak negative correlation between CSF NPTX2 values and A β 42/A β 40 ratio. In the iNPH subjects in our study, it appears that NPTX2 levels do not reflect neurodegeneration seen in other neurodegenerative disorders where lower levels are pathological. This could potentially be due to impaired clearance of NPTX2 from the interstitial and CSF compartments. However, there was no correlation between EI, a surrogate marker for ventriculomegaly and levels of NPTX2. Further studies including more accurate measures of ventricular volume are needed to evaluate this hypothesis.

Age in iNPH has been suggested to be a potential risk factor, as the prevalence of iNPH increases substantially with age [30]. Age-related changes in the brain, such as increased

vascular pathology, may contribute to the development and progression of iNPH [31]. Overall, age plays a role in the manifestation and treatment response of iNPH, highlighting the need for age-specific considerations in the management of this condition. Our study demonstrated that CSF NPTX2 concentrations had no significant correlation with age in our cohort.

The TUG test is a widely used assessment tool for evaluating gait and balance, particularly in the elderly population [32]. It is a fast and easy-to-administer test that has been validated for screening the risk of falls among elderly individuals [32]. The TUG test measures the time it takes for an individual to stand up from a chair, walk a set distance, turn around, and sit back down [33]. This has been shown to be reliable, cost-effective, safe, and time-efficient for evaluating overall functional mobility [33]. Additionally, a systematic review examined the diagnostic utility of simple tests, including an improvement in the total time to complete the TUG test post-CSF drainage in adults with iNPH [34]. The review also highlighted the diagnostic value of the improvement in TUG test completion time in identifying potential responders to shunt surgery.

Our study aimed to discern if NPTX2 concentrations correlated with performance on the TUG test at baseline and post-shunt surgery. We saw a significant, though weak, negative correlation between CSF NPTX2 values and baseline performance on the TUG. However, there was no significant correlation between CSF NPTX2 values and post-shunt TUG test performance evaluated at a median of two years post-shunt insertion.

The strengths of our study include a large cohort size, a long duration of follow-up, and the use of multiple biomarkers that reflect pathologies common in ageing. However, there are significant limitations to our study. Firstly, the study was limited to a single tertiary care centre and the patient referral pattern may not reflect the types of iNPH patient seen at other centres. Secondly, we did not evaluate other well-established markers of synaptic degeneration including SNAP25, neurogranin and GAP-43. Lastly, we do not have cognitive outcomes on patients who underwent shunt surgery because MoCA testing is not standard practice after shunting unless patients have cognitive symptoms.

Overall, our findings from this study reinforce the published literature demonstrating correlations of NPTX2 concentrations with pTau-181 concentrations, although NPTX2 does not correlate with cognition in iNPH unlike other neurodegenerative disorders such as AD and FTD.

Clinical implications and future directions

The identification of CSF biomarkers for iNPH would allow clinicians to differentiate iNPH from other neurological diseases, although it is difficult to determine which biomarkers are relevant to the iNPH population. Furthermore, the selection

of patients for shunt surgery as a treatment of iNPH must be evaluated by both short-term improvement and a more sustained long-term improvement after shunt placement.

NPTX2 did not demonstrate strong promise as a diagnostic biomarker in the iNPH population, and was not a predictive biomarker of short-term improvement after CSF drainage through TT or ELD procedures.

NPTX2 also did not predict long-term improvement post-shunt surgery. The lack of synaptic injury in iNPH also reinforces the paradigm that iNPH is a subcortical process and could explain the reversibility of cognitive impairment given the preservation of synaptic structure.

The potential role played by synaptic degeneration in aetiological subtypes, especially compensated congenital hydrocephalus manifesting in mid-life or late-life with iNPH like symptoms, requires further study.

Article information

Data availability statement: *Original contributions presented in the study are included in both the article and as Supplementary Materials. Any further inquiries may be directed to the Corresponding Author, Dr. Abhay Moghekar.*

Ethics statement: *Patients provided written informed consent for biospecimen banking for research under a Johns Hopkins IRB-approved protocol (IRB Application Number: NA_00029413).*

Authors' contributions: *MP compiled data for analysis and wrote manuscript; YZ performed data analysis; M-FX performed assays on collected samples; PW developed assays and contributed to data analysis; AM developed study design, oversaw study, contributed to data analysis, and contributed to writing of manuscript.*

Funding: *This study was funded by philanthropic contributions from the Lantry and Myers Family Foundations.*

Acknowledgements: *Thank you to the Lantry and Myers Family Foundations for providing funding for this research study.*

Conflicts of interest: *None.*

Supplementary material: *The Supplementary Material for this article can be found online on article's page.*

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