Predicting Cognitive Improvement in Normal Pressure Hydrocephalus Patients Using Preoperative Neuropsychological Testing and Cerebrospinal Fluid Biomarkers

Robert A. McGovern, MD [*] [‡]
Taylor B. Nelp, MD [‡]
Kathleen M. Kelly, MD [‡]
Andrew K. Chan, MD [§]
Pietro Mazzoni, MD, PhD [¶] [‖]
Sameer A. Sheth, MD, PhD [#]
Lawrence S. Honig, MD, PhD [‖]
Andrew F. Teich, MD, PhD [**]
Guy M. McKhann, II, MD [‡]

[*]Department of Neurosurgery, University of Minnesota, Minneapolis, Minnesota; [‡]Department of Neurological Surgery, Columbia University Medical Center, New York, New York; [§]Department of Neurological Surgery, University of California, San Francisco, San Francisco, California; [¶]Department of Neurology, Washington University School of Medicine, St. Louis, Missouri; [‖]Department of Neurology, Columbia University Medical Center, New York, New York; [#]Department of Neurosurgery, Baylor College of Medicine, Houston, Texas; [**]Department of Pathology and Cell Biology, Columbia University Medical Center, New York, New York

Correspondence:
Guy M. McKhann, II, MD,
Department of Neurological Surgery,
4th floor,
The Neurological Institute,
Columbia University Medical Center,
710 W 168th St.,
New York, NY 10032.
E-mail: gm317@columbia.edu

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BACKGROUND: Though it is well known that normal pressure hydrocephalus (NPH) patients can cognitively improve after ventriculoperitoneal shunting (VPS), one of the major dilemmas in NPH is the ability to prospectively predict which patients will improve.
OBJECTIVE: To prospectively assess preoperative predictors of postshunt cognitive improvement.
METHODS: This was a prospective observational cohort including 52 consecutive patients with approximately 1-yr follow-up. Patients underwent neuropsychological testing at baseline, postlumbar drainage, and postshunt. Cerebrospinal fluid (CSF) biomarkers and cortical biopsies were also collected to examine their relationship with postshunt cognitive improvement.
RESULTS: Rey Auditory Verbal Learning Test-L (RAVLT-L) was the only neuropsychological test to demonstrate statistically significant improvement both postlumbar drain and postshunt. Improvement on the RAVLT-L postlumbar drain predicted improvement on the RAVLT-L postshunt. Patients with biopsies demonstrating Aβ+ Tau+ had lower ventricular CSF Aβ42 and higher lumbar CSF pTau compared to Aβ– Tau– patients. A receiver operating curve analysis using lumbar pTau predicted Aβ+ Tau+ biopsy status but was not related to neuropsychological test outcome.
CONCLUSION: The RAVLT can be a useful preoperative predictor of postoperative cognitive improvement, and thus, we recommend using the RAVLT to evaluate NPH patients. CSF biomarkers could not be related to neuropsychological test outcome. Future research in a larger patient sample will help determine the prospective utility of CSF biomarkers in the evaluation of NPH patients.

KEY WORDS: Cognition, CSF biomarkers, Neuropsychology, Normal pressure hydrocephalus, Prospective cohort, Rey Auditory Verbal Learning Test

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Normal pressure hydrocephalus (NPH) is a condition usually found in the elderly and is characterized by gait dysfunction, cognitive decline, and urinary incontinence. NPH patients typically undergo a trial of cerebrospinal fluid (CSF) drainage via large volume lumbar puncture or lumbar drain over several days to assess improvement in each of the 3 major symptom groups. Although protocols for selecting surgical candidates vary across institutions, in general, if the patient improves in any combination of symptom groups, he/she is

ABBREVIATIONS: Aβ42, A$\beta_{(1\text{-}42)}$ peptide; **ANOVA,** analysis of variance; **CSF,** cerebrospinal fluid; **MMSE,** Mini-Mental Status Examination; **NPH,** normal pressure hydrocephalus; **pTau,** phospho-tau; **RAVLT,** Rey Auditory Verbal Learning Test; **ROC,** receiver operating characteristic; **tTau,** total tau; **VAS,** ventriculoatrial shunting; **VPS,** ventriculoperitoneal shunting

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considered a candidate for ventriculoperitoneal or ventriculoatrial shunting (VPS/VAS).

Gait and balance are the most common symptoms to improve after both temporary and permanent CSF diversions,[1,2] whereas cognition is generally recognized as the least likely symptom to improve in NPH.[1,2] In addition, although there are many objective neuropsychological measures of cognition that can be tested in NPH patients, it is difficult to know which tests performed preoperatively are most valuable at predicting postoperative cognitive improvement. The cognitive deficits seen in NPH typically involve multiple domains of neuropsychological testing including global function,[3,4] executive functioning,[5,6] short-term memory and learning,[7,8] psychomotor speed,[6,9] and spatial and perceptual ability.[10] A recent meta-analysis has demonstrated that NPH patients specifically appear to improve in global function, learning and memory, and psychomotor speed after VPS.[10]

Objectives

A major practical dilemma in NPH, however, is how to predict which NPH patients will improve in these cognitive measures after CSF diversion. There have been very few studies that have attempted to predict cognitive improvement post-VPS solely based on pre-VPS testing,[7,9] and there are no guidelines regarding the cognitive evaluation of these patients.

Therefore, we attempted to examine this question with 3 separate analyses. First, we wanted to prospectively determine if improvement on neuropsychological testing after CSF lumbar drainage could predict post-VPS cognitive improvement. For this analysis, we used a short battery of neuropsychological tests that probed the typical cognitive deficits seen in NPH, including the Rey Auditory Verbal Learning Test (RAVLT). This test has been shown to improve in NPH patients post-VPS[11] and is able to be completed by almost all NPH patients.[12]

Second, we wanted to study if the absence of neurodegenerative pathology on cortical biopsies taken from NPH patients could predict post-VPS cognitive improvement. Finally, we planned to try to predict a patient's cortical biopsy result based solely on preoperative CSF biomarkers. Although the importance of CSF biomarkers in the diagnosis of NPH remains unclear,[13] their theoretical value lies in their ability to do the following: (1) reflect the severity of cerebral beta-amyloid plaque and tau pathology; and (2) predict the presence or absence of cognitive improvement. More specifically, value thresholds of $A\beta_{(1\text{-}42)}$ peptide ($A\beta42$), total tau (tTau), and phospho-tau levels (pTau) have been used to attempt to differentiate between Alzheimer's disease and other forms of dementia.[14] In this fashion, then, a patient's preoperative neuropsychological and CSF biomarker testing results could provide a window into the likely postoperative cognitive outcomes for NPH patients.

METHODS

Study Design, Setting, and Participants

This was a prospective, observational study performed at a single academic medical center. Fifty-two consecutive patients were enrolled in the study from January 2011 to January 2015. All portions of this protocol were approved by our internal institutional review board. Patients were clinically diagnosed with possible or probable NPH. Once diagnosed, patients underwent the typical clinical NPH evaluation protocol practiced at our institution (see **Methods**, **Supplemental Digital Content 1** for specifics on the diagnosis and evaluation protocol used at our institution).

Outcome Variables and Data Sources

As part of this research protocol, patients underwent a Mini-Mental Status Examination (MMSE),[15] Rey Auditory Verbal Learning Test (RAVLT),[16,17] Stroop test, and Grooved Pegboard testing (Lafayette Instrument Company, Lafayette, Indiana) prior to placement of the lumbar drain (see **Methods**, **Supplemental Digital Content 1** for details on testing). Upon placement of the lumbar drain in the afternoon of the first hospital day, CSF was sent for $A\beta42$, tTau, and pTau levels as part of our standard clinical protocol. CSF was collected in the usual, sterile manner and sent to a reference laboratory (Athena Diagnostics, Worcester, Massachusetts) for determination of $A\beta42$, tTau, and pTau concentrations. Protein concentrations were performed via enzyme-linked immunosorbent assay and determined from standard curves using synthetic β-amyloid(1-42) peptide, recombinant human total tau protein, and a synthetic 34-amino acid protein phosphorylated at the position equivalent to threonine-181 in the tau protein. Concentrations are reported in picograms per milliliter.

After placement of the lumbar drain, patients typically underwent CSF drainage every 2 h for the next 48 to 60 h. On the morning of the fourth hospital day, the lumbar drain was removed, and the patient underwent the same movement and cognitive testing that he/she performed at baseline. After being discharged home, the patient typically met the treating neurosurgeon in the office 1 to 2 wk later, where they discussed potential VPS placement.

All VPS were placed by the 2 participating neurosurgeons (G.M.M. and S.A.S.). The decision to place the VPS was based solely on typical clinical practice (see **Methods**, **Supplemental Digital Content 1**). If the patient underwent VPS, CSF was again sent for $A\beta42$, tTau, and pTau upon placement of the proximal shunt catheter. As part of our standard clinical protocol for consenting patients, a small frontal cortical brain biopsy was also performed and sent to neuropathology for evaluation (see **Methods**, **Supplemental Digital Content 1**). For beta-amyloid immunostains, the results were reported as few/rare, moderate, or frequent/severe intracellular plaques. Tau immunostains almost never showed tau-positive neurons. However, tau-positive dystrophic neurites were occasionally seen, usually described as few/rare, although a minority of biopsies reported more frequent dystrophic neurites. For the purposes of this paper, we have classified any positive tau immunostaining as a positive result, which allows for 4 groups: $A\beta-$ Tau–, $A\beta+$ Tau–, $A\beta-$ Tau+, and $A\beta+$ Tau+.

Postoperative adjustments to the VPS valve settings were performed solely on the discretion of the treating neurosurgeon to optimize the patient's clinical status (see **Methods**, **Supplemental Digital Content 1**). The research team then followed up with the patient in the office at follow-up visits to perform cognitive testing as described above. We

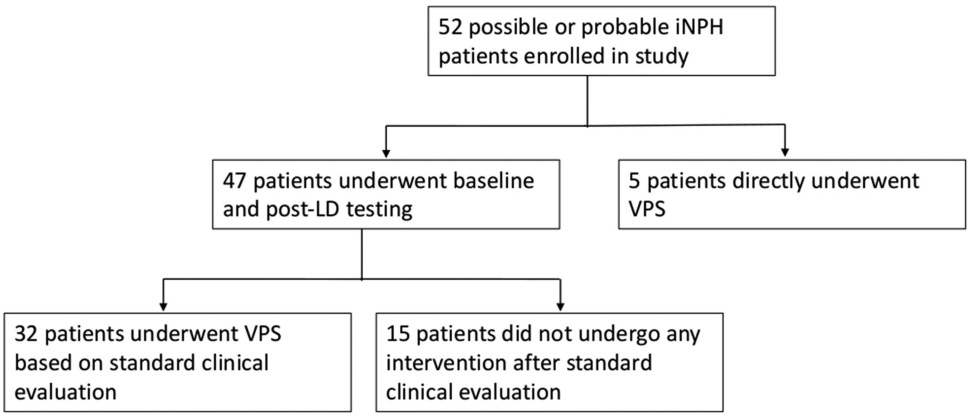

FIGURE 1. *Flow diagram illustrating patient enrollment.*

used the most recent follow-up visit as the post-VPS evaluation in this study. Every patient undergoing VPS was able to complete testing at one follow-up visit. Some patients were unable to complete every test at each visit, and so, incomplete tests were excluded from their test-specific data analysis when this occurred.

Statistical Methods

To examine group differences in neuropsychological testing, we initially applied 1-way analysis of variance (ANOVA) to the baseline, post-LD, and post-VPS groups for all of the neuropsychological tests mentioned above. Prior to the beginning of the study, we made a number of prespecified hypotheses based on prior research (see **Methods**, **Supplemental Digital Content 1**). We thus applied 1-sided *t*-tests to these group comparisons based on these prespecified hypotheses. We applied the same *t*-test methodology to RAVLT-L subgroup analysis (responders vs nonresponders).

We used a logistic regression model to attempt to predict post-VPS cognitive improvement on the RAVLT-L. Because of the number of variables included in the multivariate analysis relative to the number of observations, we initially performed a nonlinear iterative partial least-squares analysis to prevent multicollinearity in the final analysis (see **Methods**, **Supplemental Digital Content 1** for details on this analysis). A least-squares multivariate logistic regression model was then used to attempt to predict post-VPS RAVLT-L improvement.

When examining the relationship of biopsy status to cognitive improvement on neuropsychological tests, prior research allowed us to make some prespecified hypotheses (see **Methods**, **Supplemental Digital Content 1**). For these hypotheses, we used *t*-tests to compare groups. For all other groups, we used Tukey–Kramer honest significant difference (HSD) tests to correct for multiple comparisons.

Similarly, when examining CSF biomarker results, we made prespecified hypotheses based on prior research but used nonparametric tests (Wilcoxon–Mann–Whitney) tests to compare these groups (see **Methods**, **Supplemental Digital Content 1**). For all other comparisons, we initially used Wilcoxon/Kruskal–Wallis rank sums tests to assess for any difference among all the groups and then the Dunn method to compare all other group combinations to correct for multiple comparisons.

All statistical evaluations, including ANOVA, *t*-test, Tukey–Kramer HSD, and receiver operating characteristic (ROC) curves, were completed in JMP 12.1.0 (SAS Institute, Cary, North Carolina). A P value of $<.05$ was prospectively taken to indicate a statistically significant difference for all statistical evaluations. Figures were prepared using a combination of JMP 12.1.0 and GNU Image Manipulation Program 2.8.18 (https://www.gimp.org).

RESULTS

Participants and Descriptive Data

Figure 1 shows a flow diagram of how the 52 patients were enrolled. Of the 47 patients who underwent both baseline and post-LD neuropsychological testing, 32 had VPS placed. There were no differences in either baseline neuropsychological testing or changes in testing post-LD (Table 1) between patients who had a VPS placed and those who did not. Patients who were shunted, however, did demonstrate improvement after lumbar drainage in the gait subscore of the Unified Parkinson Disease Rating Scale compared to patients who were not shunted (Table 1), indicating that changes in gait likely comprised much of the decision-making process.

Main Results

Table 2 shows the demographics and neuropsychological testing of our patient population.

The only neuropsychological test that statistically improved post-LD or post-VPS was the RAVLT-L (Table 2, Figure 2A). Importantly, the change in RAVLT-L score post-LD correlated with change in RAVLT-L score post-VPS (Figure 2B; $R^2 = 0.43$, $P = .015$). The mean follow-up time for patients was 314 d (+221 d).

Similar to prior studies,[7] the distribution of RAVLT-L improvement in our cohort demonstrated a right-skewed normal distribution, with some patients demonstrating large improvements (maximum 25 points, minimum –8, median 3) and

TABLE 1. Univariate Analysis of Clinical Variables and Neuropsychological Test Scores Split by Patients Who Underwent VPS

Variable	No VPS N = 15	VPS N = 32	P value
Sex (M:F)	7:8	19:13	.41
Mean age, yr (±SD)	76.1 (±5.2)	76.2 (±6.7)	.94
Mean UPDRS gait score, points (±SD)	1.7 (±1)	1.7 (±1)	.89
Mean UPDRS gait score change post-LD, points (±SD)	0.3 (±0.8)	−0.4 (±0.7)	.0098
Mean UDI-6 incontinence score, points (±SD)	6.1 (±4)	5.6 (±3)	.73
Mean UDI-6 score change post-LD, points (±SD)	−0.1 (±1)	−0.6 (±1)	.61
Mean MMSE score, points (±SD)	26.1 (±3.9)	26.4 (±3)	.82
Mean MMSE score change post-LD, points (±SD)	0.2 (±3)	0.5 (±4)	.77
Mean Stroop interference ratio (±SD)	1.70 (±1.1)	2.09 (±1.4)	.44
Mean Stroop ratio change post-LD (±SD)	0.14 (±0.9)	0.02 (±1.3)	.79
Mean RAVLT-L score, points (±SD)	24.7 (±8)	22.8 (±7.5)	.49
Mean RAVLT-L change post-LD, points (±SD)	0.5 (±6)	5.1 (±8)	.09
Mean RAVLT-I score, points (±SD)	2.7 (±2)	2.9 (±2)	.80
Mean RAVLT-I change post-LD, points (±SD)	0.6 (±2)	0.2 (±2)	.64
Mean RAVLT-D score, points (±SD)	1.3 (±2)	1.6 (±2)	.65
Mean RAVLT-D change post-LD, points (±SD)	0.4 (±2)	0.6 (±2)	.79
Mean dominant hand Grooved Pegboard score, s (±SD)	198.5 (±61)	187.2 (±74)	.64
Mean dominant hand Grooved Pegboard score change post-LD, s (±SD)	−3.8 (±70)	−4.2 (±41)	.99
Mean nondominant hand Grooved Pegboard score, s (±SD)	242.9 (±68)	225 (±80)	.52
Mean nondominant Grooved Pegboard score change post-LD, s (±SD)	−14.3 (±38)	4.0 (±40)	.29

F, female; LD, lumbar drainage; M, male; MMSE, Mini-Mental Status Examination; RAVLT-D, Rey Auditory Verbal Learning Test-D; RAVLT-I, Rey Auditory Verbal Learning Test-I; RAVLT-L, Rey Auditory Verbal Learning Test-L; SD, standard deviation; UDI-6, Urinary Distress Inventory-6; UPDRS, Unified Parkinson Disease Rating Scale; VPS, ventriculoperitoneal shunting.

TABLE 2. Demographic and Neuropsychological Testing Characteristics of Patients at Each Study Time Point

	Baseline N = 47	Post-LD N = 47	Post-VPS N = 32	P value
Sex (M:F)	27:20	27:20	18:14	>.99
Mean age, yr (±SD)	76.7 (±6.1)	76.7 (±6.1)	76.4 (±6.7)	.98
Mean UPDRS gait score, points (±SD)	1.7 (± .9)	1.4 (±0.9)	.8 (±0.8)	.0012
Mean UDI-6 incontinence score, points (±SD)	5.6 (±3.4)	5.1 (±3.5)	6.4 (±3.5)	.52
Mean MMSE score, points (±SD)	26.4 (±3.1)	26.5 (±3.9)	27.1 (±2.8)	.77
Mean Stroop interference ratio (±SD)	1.98 (±1.3)	2.1 (±1.5)	1.72 (± 1.1)	.66
Mean RAVLT-L score, points (±SD)	23.4 (±7.5)	27.6 (±10)	31.4 (±10)	.0078
Mean RAVLT-I score, points (±SD)	2.8 (±2.4)	3.3 (±2.6)	3.7 (±3.5)	.49
Mean RAVLT-D score, points (±SD)	1.6 (±1.8)	2.1 (±2.3)	2.9 (±3.1)	.11
Mean dominant hand Grooved Pegboard score, s (±SD)	187 (±67)	177 (±69)	168 (±73)	.61
Mean nondominant hand Grooved Pegboard score, s (±SD)	228 (±76)	224 (±72)	198 (±69)	.37

F, female; LD, lumbar drainage; M, male; MMSE, Mini-Mental Status Examination; RAVLT-D, Rey Auditory Verbal Learning Test-D; RAVLT-I, Rey Auditory Verbal Learning Test-I; RAVLT-L, Rey Auditory Verbal Learning Test-L; SD, standard deviation; UDI-6, Urinary Distress Inventory-6; UPDRS, Unified Parkinson Disease Rating Scale; VPS, ventriculoperitoneal shunting.

others none or worsening post-LD (Figure 2C). Because of this, we next split the patients into 2 groups (responders and nonresponders) based on a >3-point improvement in RAVLT-L performance post-LD. Of note, because patients were primarily shunted based on gait symptoms, there were similar numbers of patients in each group. Patients who improved after lumbar CSF drainage (responders) saw a mean 9.7-point increase in their RAVLT-L score compared to baseline. Postoperatively, these patients demonstrated a 12.3-point improvement post-VPS (Figure 2D). On the other hand, nonresponders worsened by 2.3 points post-LD and improved by 3.3 points post-VPS (Figure 2D). Importantly, there was no difference in baseline RAVLT-L scores between responders and nonresponders (**Figure**, **Supplemental Digital Content 2**).

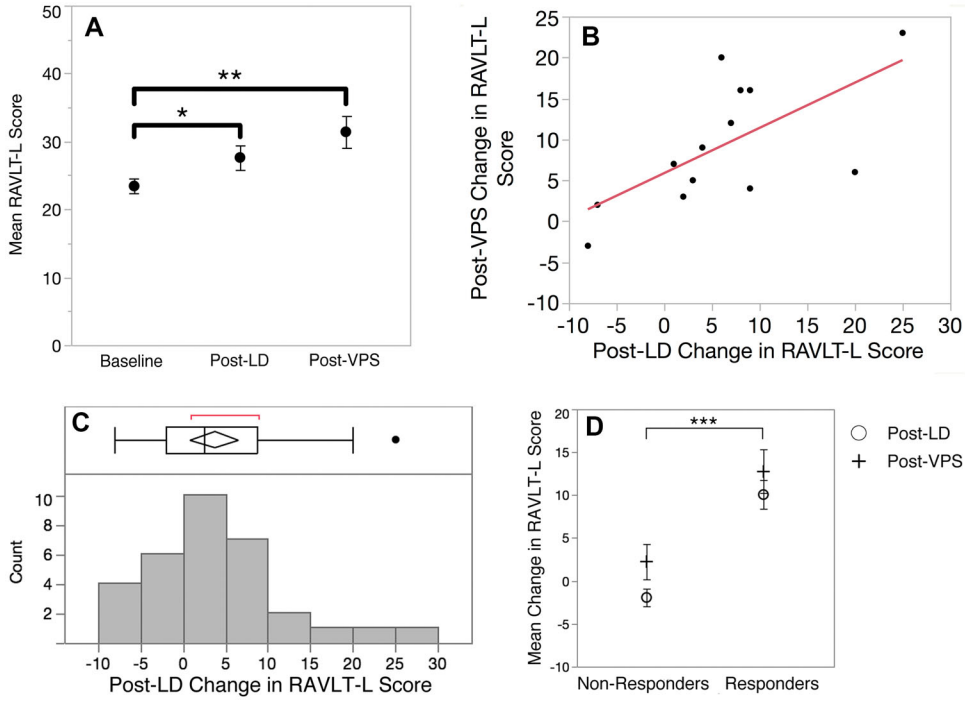

FIGURE 2. *Rey Auditory Verbal Learning Test-Learning (RAVLT-L) scores for NPH patients.* **A**, *Mean RAVLT-L raw score significantly improves both post-LD and post-VPS compared to baseline testing.* $^{*}P = .047$, $^{**}P = .0031$, *1-sided t-test.* **B**, *Post-VPS RAVLT-L improvement is correlated with post-LD RAVLT-L improvement in a linear fashion* ($R^2 = 0.43$, $P = .015$). **C**, *RAVLT-L improvement after lumbar CSF drainage (post-LD) follows a right-skewed normal distribution.* **D**, *When split into 2 groups based on RAVLT-L improvement (>3 points) post-LD, responders demonstrated a significant difference in RAVLT-L score post-VPS.* $^{***}P < .0001$, *2-sided t-test.*

Finally, we created a multivariate logistic regression model to predict post-VPS cognitive improvement. We included a number of preoperative variables in the initial partial least-squares model to select the final variables to include in the final model (**Figure**, **Supplemental Digital Content 3**). Only post-LD RAVLT-L improvement significantly predicted post-VPS RAVLT-L improvement in the final model (**Table**, **Supplemental Digital Content 4**).

Prospective Analysis of CSF Biomarkers, Biopsy Pathology, and Cognitive Improvement

We split our patients into 4 groups based on their cortical biopsy results: Aβ– Tau–, Aβ+ Tau–, Aβ– Tau+, and Aβ+ Tau+. None of the groups demonstrated any statistically significant differences in neuropsychological testing when correcting for multiple comparisons. When analyzing CSF biomarkers within the context of cortical biopsy results, we found that ventricular Aβ42 was significantly lower in Aβ+ Tau+ patients when compared to Aβ– Tau– patients (Table 3; Wilcoxon–Mann–Whitney, $P = .05$) whereas lumbar pTau values were significantly higher (Table 3, Wilcoxon–Mann–Whitney, $P = .043$). We next performed an ROC analysis to predict the presence of Aβ+ Tau+ pathology using only lumbar pTau values. For these patients, the area under the curve was 0.79 (Figure 3), with an optimal pTau value of 34.7 pg/mL (**Table**, **Supplemental Digital Content 5**). At this level, the sensitivity of pTau for predicting Aβ+ Tau+ biopsy status was 100%, and specificity was 62% (Figure 3).

DISCUSSION

Key Results

Our prospective observational study demonstrates that NPH patients performed significantly better on the RAVLT-L after lumbar CSF drainage. An individual patient's change in RAVLT-L score post-LD correlated with his/her change in RAVLT-L score post-VPS. We split NPH patients into 2 groups consisting of patients who improved after lumbar drainage (responders) and those who did not (nonresponders). Responders improved their RAVLT-L scores by approximately 10 words postoperatively compared to nonresponders, whereas baseline RAVLT-L scores did not differ between the 2

TABLE 3. CSF Biomarkers in Relation to Biopsy Status

CSF Biomarker	Cortical Biopsy Pathology				*P* value
	Aβ− Tau− *N* = 13	Aβ− Tau+ *N* = 1	Aβ+ Tau− *N* = 11	Aβ+ Tau+ *N* = 7	
Mean ventricular CSF Aβ42, pgmL (±SD)	527 (±197)	532.8	431 (±177)	335 (±154)	.18
Mean lumbar CSF Aβ42, pg/mL (±SD)	330 (±173)	574	348 (±272)	280 (±79)	.63
Mean ventricular CSF tTau, pg/mL (±SD)	737 (±818)	2495	426 (±471)	962 (±983)	.07
Mean lumbar CSF tTau, pg/mL (±SD)	162 (±102)	182	200 (±88)	378 (±348)	.18
Mean ventricular CSF pTau, pg/mL (±SD)	46.9 (±30.2)	61.3	35.6 (±18.9)	52 (±27.4)	.53
Mean lumbar CSF pTau, pg/mL (±SD)	27.5 (±10)	37.8	37 (±16.6)	48.6 (±21.8)	.13

ANOVA, analysis of variance; CSF, cerebrospinal fluid; pTau, phospho-tau; tTau, total tau; SD, standard deviation.
Although ANOVA did not demonstrate a significant difference between groups, prior research (see **Supplemental Digital Content 1**) allowed us to hypothesize a priori that Aβ+ Tau + patients would have higher CSF pTau and tTau levels and lower Aβ42 levels than Aβ− Tau− patients. This allowed us to make direct comparisons between these 2 groups.

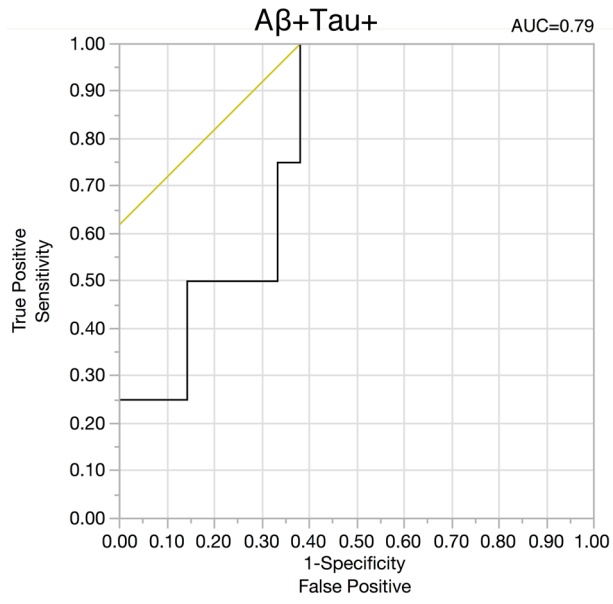

FIGURE 3. *Receiver operating curve analysis for Aβ+ Tau+ pathology using lumbar CSF pTau levels.*

groups. A multivariate logistic regression demonstrated that only RAVLT-L improvement after lumbar CSF drainage could predict post-VPS improvement. No other neuropsychological tests were helpful in determining cognitive improvement either post-LD or post-VPS. CSF ventricular Aβ42 was significantly lower and lumbar pTau significantly higher in Aβ+ Tau+ patients when compared to Aβ− Tau− patients. Lumbar pTau was able to predict Aβ+ Tau+ biopsy status with a high sensitivity and moderate specificity, but we were unable to correlate biopsy status with neuropsychological outcomes.

The RAVLT is a multifaceted test that attempts to measure different aspects of verbal learning and memory.[17] A recent meta-analysis has demonstrated that NPH patients consistently demonstrate improvement on the RAVLT-L (short/immediate term recall) and RAVLT-D (delayed recall) post-VPS.[11,12,18,19] However, although many studies have demonstrated that NPH patients can improve after shunting on a multitude of neuropsychological tests, a major clinical problem in NPH remains how to predict which patients will improve post-VPS solely based on preoperative testing. Here, we show that the RAVLT-L is a test that can predict post-VPS improvement based on post-LD improvement. In addition, unlike some prior studies that have shown that post-VPS improvement relies mainly on baseline cognitive function,[9,20] we did not see any differences in baseline RAVLT-L scores between NPH responders and nonresponders. This indicated to us that even patients with relatively poor baseline cognition have the ability to improve after VPS as long as they demonstrate improvement post-LD.

The European multicenter NPH study has shown that the RAVLT is its most "useful" test in that the largest proportion of NPH patients are able to complete the RAVLT when compared to other neuropsychological tests.[12] Indeed, the reality of clinical practice necessitates that neurologists and neurosurgeons choose a limited number of tests to include in their evaluation of possible or probable NPH patients. Given its ease of use and ability to predict cognitive improvement, the RAVLT appears to be an ideal candidate for assessing NPH patients throughout the pre- and postoperative period.

CSF biomarkers remain an important consideration in the evaluation of NPH, although their clinical significance remains unclear. First, a number of large studies have shown that NPH patients with Aβ pathology on cortical biopsies typically demonstrate lower levels of lumbar and ventricular CSF Aβ42.[4,21-23] We partially confirmed this association as Aβ+ Tau+ patients had lower ventricular CSF Aβ42 compared to Aβ− Tau− patients. Similarly, the fraction of phospho-tau-immunostained tissue has

been shown to correlate well with increasing pTau in lumbar and ventricular CSF.[4] Again, we confirmed that Aβ+ Tau+ patients had higher lumbar pTau levels when compared to Aβ– Tau– patients. It is important to note here that although many prior retrospective studies have demonstrated similar findings, we were able to confirm this finding without the confounder of selection bias. Moreover, these studies typically only include group means, making it difficult to apply this research to an individual patient. We therefore performed an ROC analysis for lumbar pTau to predict an individual's Aβ+ Tau+ status. This analysis demonstrated that pTau levels above 34.7 pg/mL would include all Aβ+ Tau+ patients (100% sensitivity) but would also include a fair number of other patients (62% specific) with a negative predictive value of 100% but a positive predictive value of only 33%.

Second, the more controversial issue related to biopsy status in NPH patients relates to whether or not patients with more severe pathology still retain the capacity to cognitively improve with VPS. Some studies have been able to correlate an increased fraction of immunostained Aβ tissue with worsened MMSE performance,[4] whereas others have shown that patients with Aβ+ Tau+ pathology do not improve with VPS.[24] We were unable to show any difference between NPH patients based on biopsy status on any of the neuropsychological tests given. Although this may be related to the sample size available, there did not appear to be any trends when we split patients into the 4 biopsy groups. Therefore, in a small sample size, our patients who were Aβ+ Tau+ appeared to retain the ability to cognitively improve, particularly on the RAVLT-L.

We therefore propose that the first priority in evaluating an NPH patient should be RAVLT testing. If the patient improves by approximately 5 to 10 words on the RAVLT-L portion after lumbar CSF drainage, one can likely expect post-VPS cognitive improvement regardless of other factors. As a subsequent option, lumbar CSF pTau can be sent and evaluated. If the patient's pTau is less than 35 pg/mL, it is fair to say that the patient is unlikely to have Aβ+ Tau+ pathology (negative predictive value, 100%). Prior research would indicate that these patients may be more likely to improve cognitively post-VPS, but we are unable to confirm that in this study.

This protocol will likely be helpful in specific circumstances when managing NPH patients. For example, when evaluating a patient who does not clearly improve in gait/balance, but does improve on the RAVLT-L, the evaluating neurosurgeon may consider shunting purely for cognitive improvement. Two of the 15 patients in our study who did not undergo VPS improved by 9 and 11 words on the post-LD RAVLT-L, indicating they likely would have significantly improved cognitively post-VPS. These patients were not shunted because their gait did not improve post-LD, and the patients did not subjectively "feel" an improvement in cognition. Interestingly, though the RAVLT appears to be one of the best objective measures of cognitive improvement in NPH patients, it does not correlate with patients' subjective feelings on cognitive improvement as well as measures of visual memory.[7]

Limitations

There are a number of limitations to this study. The main limitation is the sample size of this study. This may partially explain the weak association between CSF biomarkers and biopsy status as well as our inability to demonstrate statistically significant correlations between our neuropsychological testing and our cortical biopsy results. Although reflective of the reality of clinical practice, another limitation is that only 32 of the 47 patients with baseline neuropsychological testing underwent VPS that could act as a confounder. Unsurprisingly, when we compared these 2 groups, they differed only in gait improvement after lumbar drainage. In other words, the patients who did not undergo VPS did not improve in gait post-LD. Because all of the neuropsychological test scores were similar, however, these 32 patients should be representative of the group as a whole. In addition, because we needed to limit our cognitive testing to a short battery, there are other measures that may have shown significant differences but were not included in this study. Alternatively, some tests, such as the MMSE, may have suffered from a ceiling effect, as our specific patient population had a quite high mean baseline score (26.0). Regardless, each neuropsychological test used in an evaluation has its own limitations[25] and should be taken into account when deciding how to evaluate NPH patients. Finally, we have purposely limited the scope of our study to the cognitive realm of NPH and ignored the relevance of gait and balance issues. Thus, although our study is meant to solely evaluate the cognitive improvement seen in NPH, it is important to acknowledge the primacy of gait and balance improvement in the decision-making process for NPH patients. Despite these limitations, the prospective observational nature of our study along with its predefined hypotheses gives these conclusions more impact when applied to the evaluation and care of NPH patients.

CONCLUSION

Interpretation

The RAVLT can be a useful preoperative predictor of postoperative cognitive improvement, and thus, we recommend using the RAVLT to evaluate NPH patients. Future research in a larger patient sample will help determine the prospective utility of CSF biomarkers in the evaluation of NPH patients.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Supplemental Digital Content 1. Methods. Methods expands on 3 aspects of the study: (1) the clinical decision-making process with regards to placement of VPS in NPH patients, (2) details of the neuropsychological tests used, and (3) rationale for the prespecified statistical hypotheses.
Supplemental Digital Content 2. Figure. Comparison of mean baseline RAVLT-L scores between responders and nonresponders.
Supplemental Digital Content 3. Figure. Variable importance plots of potential *X* variables in a logistic regression model to explain post-VPS improvement in RAVLT-L scores.
Supplemental Digital Content 4. Table. Terms and parameter estimates of logistic regression model to predict post-VPS RAVLT-L improvement.
Supplemental Digital Content 5. Table. Receiver operating curve table for Aβ+ Tau+ pathology using lumbar CSF pTau levels.

COMMENT

This is an interesting and important study, as cognitive functioning following normal pressure hydrocephalus shunting has had variable outcomes. Having predictive measures of outcome would be of great value to providers and patients regarding risks and benefits of surgical intervention. The study was well designed, and the prospective and consecutive nature of the study design makes for a stronger design than in prior studies examining cognitive outcome from normal pressure hydrocephalus shunting. The most significant limitation of the study was the small sample size, which the authors acknowledge in the conclusions section.

Suzanne Penna
Atlanta, Georgia