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Lack of Shunt Response in Suspected Idiopathic Normal Pressure Hydrocephalus with Alzheimer Disease Pathology

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Abstract

To determine the impact of cortical Alzheimer disease pathology on shunt responsiveness in individuals treated for idiopathic normal pressure hydrocephalus (iNPH), 37 patients clinically diagnosed with iNPH participated in a prospective study in which performance on neurologic, psychometric, and gait measures before and 4 months after shunting was correlated with amyloid β plaques, neuritic plaques, and neurofibrillary tangles observed in cortical biopsies obtained during shunt insertion. No complications resulted from biopsy acquisition. Moderate to severe pathology was associated with worse baseline cognitive performance and diminished postoperative improvement on NPH symptom severity scales, gait measures, and cognitive instruments compared to patients lacking pathology.

Although idiopathic normal pressure hydrocephalus (iNPH) is considered a reversible cause of cognitive and motor impairment in older adults, estimates of the response rate to shunting vary widely.^{1,2} One potential contributor to shunt unresponsiveness is the presence of comorbid neurologic conditions that are common in aging. The role of Alzheimer disease (AD) in patients with iNPH is debated. Whereas some data suggest that comorbid AD contributes to poorer response to shunting in patients with otherwise typical symptoms of iNPH, other evidence indicates that patients who demonstrate typical features of iNPH benefit equally from shunting regardless of the presence of AD pathology.^{3–5}

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Potential Conflicts of Interest

Dr. Lee is an inventor on a pending patent from the University of Pennsylvania concerning an antibody that recognizes oligomeric A β . He has received no money or royalties related to this patent application, and the antibody was not used in this study. Dr. Shaw has a financial stake in Saladex Biomedical and has received honoraria from Pfizer. Dr. Clark has received support from the Department of Health for the Commonwealth of Pennsylvania, Elan-Wyeth, and Bristol Myers Squibb. Drs. Shaw, Clark, and Xie have all received NIH support for work related to Alzheimer Disease.

To determine the impact of AD on the presentation and clinical course of patients being shunted for iNPH, we conducted a prospective study in which the initial features and postsurgical outcomes of patients treated for presumed iNPH were correlated with the presence of the pathologic hallmarks of AD—amyloid β (A β) plaques and tau neurofibrillary tangles—observed in cortical tissue. We hypothesized that patients with pathological evidence of AD would exhibit more severe initial symptomatology and a lesser degree of shunt responsiveness than patients lacking pathology.

Subjects and Methods

Preoperative Clinical Assessment

All participants underwent a standardized evaluation consisting of a clinical history, physical and neurologic examination, videotaped assessment of gait, and a psychometric battery. A single behavioral neurologist evaluated all patients at baseline and at follow-up.

CLINICAL SYMPTOM SCALES—Symptom severity was rated using a 15-point NPH Scale reported in prior investigations⁶ and consisting of 3 5-point subscales describing deficits in gait, cognition, and bladder control. Total scores ranged from 3 (profoundly impaired) to 15 (normal).

GAIT MEASURES—Patients walked 25 feet, made a single 180° turn, and returned 25 feet to their starting point (50 feet total). Three parameters were assessed: (1) time to walk 50 feet (in seconds), (2) number of steps required to turn, and (3) overall quality of gait as judged by the physician on a 5-point scale ranging from 0 (normal) to 4 (nonambulatory). Similar gait measures have been described.⁷

COGNITIVE EVALUATION—The psychometric battery included: the Wechsler Memory Scale (3rd ed) logical memory subtest, a 10-item word list recall task, digit span forward and reversed, category fluency, Boston Naming Test (first 30 items), trail making (A & B; total time and errors), digit symbol, and clock draw and copy.⁸ This battery resembles those used in other studies of iNPH.⁶ Patient performance was compared to that of 202 age- and education-matched normal control subjects who participate in research at the Penn Memory Center; Z scores were computed for patient performance on each instrument, expressed as standard deviations from the mean of control performance. The average Z score across instruments (composite Z score) was employed as a global measure of cognition.⁹

Diagnosis of iNPH and Study Enrollment

This study was approved by the institutional review board at the University of Pennsylvania. All patients and their designated representatives signed informed consent prior to participation. Enrolled patients were diagnosed with possible iNPH by the participating behavioral neurologist, who remained masked to their biopsy results. Enrolled patients were between the ages of 50 and 79 years (inclusive) and exhibited: (1) presence of 2 of the following symptoms or signs: (a) a progressive “magnetic” gait impairment, (b) progressive urinary incontinence, and (c) progressive cognitive impairment; and (2) ventriculomegaly on head computed tomography or brain magnetic resonance imaging out of proportion to generalized atrophy with an Evans’ index ≥ 0.3 .¹⁰ Patients with other neurologic or psychiatric conditions—including secondary causes of NPH—were excluded, as were patients with severe cognitive impairments that precluded meaningful psychometric evaluation. The clinical history, gait, and imaging findings of these patients were consistent with published guidelines for diagnosing iNPH.¹¹ Because formal demonstration of normal cerebrospinal fluid (CSF) opening pressure by lumbar puncture was not a necessary criterion for inclusion in this study, patients met guideline criteria for possible rather than probable iNPH. Over a 33-month period, 78 individuals were referred

for evaluation; 47 were diagnosed with iNPH and underwent surgery, 39 met study inclusion and exclusion criteria, and 37 were enrolled and had cortical tissue analyzed after shunting. Of these 37 enrolled patients, 30 followed up and were evaluated postoperatively. Of the 7 enrolled subjects who did not follow up, 3 experienced unrelated health complications that prohibited follow-up (1 of these died), 2 experienced surgical complications from shunt placement that prevented outpatient evaluation (1 of these died), and 2 declined for reasons unrelated to their health status.

Shunting and Tissue Analysis

All shunts were placed in the right prefrontal cortex. There were no surgical complications associated with biopsy acquisition. An approximately 0.5cm³ piece of cortical tissue was biopsied at the site of shunt entry and immersion fixed in neutral buffered formalin overnight followed by paraffin embedding. Six-micrometer-thick sections were stained with hematoxylin and eosin for neuropathological examination, and with thioflavin S for identification of neuritic plaques and neurofibrillary tangles. Sections were also immunohistochemically labeled for A β plaques (NAB228, a mouse monoclonal antibody raised against A β ₁₋₁₁ synthetic peptide), ¹² hyperphosphorylated tau for neurofibrillary tangles and dystrophic neurites (PHF1), ¹³ α -synuclein for Lewy bodies and Lewy neurites (SYN303), ¹⁴ and TDP-43 for pathological inclusions (rabbit polyclonal antibody; Protein-Tech Group, Chicago, IL) with methods as previously described.¹⁵ Control sections processed without primary antibodies were included in all runs and displayed no specific staining. Sections obtained from patients with autopsy-confirmed AD were used as positive controls. Semiquantitative scores were assigned corresponding to the densities of neurofibrillary tangles and A β plaques (as assessed by immunohistochemistry), and to neuritic plaques (as assessed by thioflavin S stain). Scores were as follows: absent = 0, rare = 0.5, low = 1, moderate = 2, and high = 3 (Fig 1). Neuritic plaque scores were based on Consortium to Establish a Registry for Alzheimer's Disease criteria.

Postoperative Clinical Assessment

Study participants were assessed approximately 4 months postoperatively (mean, 120 days; standard deviation, 30 days) using the same measures employed during initial evaluation.

Statistical Analysis

Two-sample *t* tests were used to compare performance on study measures at baseline across the no pathology and moderate-to-severe pathology groups. Paired *t* tests were used to compare baseline and postoperative performance of the entire cohort. Due to variability in performance on the timed gait assessment, this measure was standardized by computing the proportion of change in gait time from baseline; this value was analyzed using a 1-sample *t* test. Repeated measures analyses of variance (ANOVAs) were performed in which group (no, mild, or moderate-to-severe tau and A β pathology) and study visit (baseline, postoperative) were factors, and performance on study measures was used as the dependent variable. An exact test was used to compare the rates of shunt responsiveness across pathology groups (shunt responsiveness was operationally defined as an improvement ≥ 2 on the NPH scale). Finally, paired *t* tests were used to compare performance across study visits for each pathology group for each measure. All analyses were done using SAS Software (version 9.2, SAS Institute, Cary, NC) and were 2-sided. For all analyses, statistical significance was set at the 0.05 level.

Results

Presence of Cortical Pathology

In the 37 patients (mean age, 75.0 years; standard deviation, 5.6 years) who underwent cortical biopsy, 25 (67.6%) demonstrated evidence of ≥ 1 AD pathologic marker, whereas 12 (32.4%)

showed no evidence of AD pathology (Table 1). Patients with AD pathologic findings were subdivided into those with mild pathology or moderate-to-severe pathology, the latter defined by the presence of all of the following: moderate-to-high amyloid plaque burden, moderate neuritic plaque burden (none had high neuritic plaque pathology), and any detectable cortical tau pathology ($n = 9$; 24.3%). Patients with moderate-to-severe pathology did not differ significantly from patients lacking pathology in either age (78.22 vs 74.25 years; $t = 1.56$, $df = 19$, $p = 0.134$) or education (14.33 vs 13.13 years; $t = 1.07$, $df = 18$, $p = 0.2974$). Six patients had findings consistent with amyloid angiopathy. No other cerebrovascular pathology or any other pathologic findings were observed.

Impact of Cortical Pathology on Baseline Performance and Shunt Responsiveness

EFFECT OF AD PATHOLOGY ON BASELINE PERFORMANCE—The no pathology group exhibited better baseline performance on the composite Z score than the moderate-to-severe pathology group ($t = 2.38$, $df = 15$, $p = 0.031$). No other significant differences were noted between groups on the NPH scale or subscales or gait measures.

RESPONSE OF ENTIRE COHORT TO SHUNTING—There was significant improvement between baseline and postoperative follow-up on the NPH scale total score ($t = 6.16$, $df = 29$, $p < 0.0001$) (Fig 2A), all of its subscales (gait, $t = 6.11$, $df = 29$, $p < 0.0001$; cognition, $t = 3.75$, $df = 29$, $p = 0.0008$; incontinence, $t = 5.07$, $df = 28$, $p < 0.0001$), quality of gait ($t = 3.53$, $df = 29$, $p = 0.0014$), proportional change in gait time ($t = 3.10$, $df = 28$, $p = 0.0044$), and composite Z score ($t = 3.99$, $df = 20$, $p = 0.0007$) (see Fig 2B).

EFFECT OF PATHOLOGY ON SHUNT RESPONSIVENESS—Repeated measures ANOVAs revealed no significant main effects of pathology on any study measures; however, there were significant 2-way interactions between study visit and pathology group on the NPH scale total ($F_{2,27} = 7.09$, $p = 0.0034$), NPH gait subscale ($F_{2,27} = 7.54$, $p = 0.0025$), and NPH cognitive subscale ($F_{2,27} = 4.02$, $p = 0.0296$). There was a strong trend toward a 2-way interaction between study visit and pathology for the composite Z score ($F_{2,18} = 3.46$, $p = 0.0534$) (see Fig 2). The proportion of patients experiencing an improvement of ≥ 2 points on the NPH scale was 6 of 8 in the no pathology group (75.0%), 12 of 14 in the mild pathology group (85.7%), and 2 of 8 in the moderate-to-severe pathology group (25.0%); the difference between groups was significant (exact test; $p = 0.014$).

Patients with no tau and A β pathology and mild tau and A β pathology showed significant ($p \leq 0.05$) improvements on the NPH scale and subscales, quality of gait, proportion of change in gait speed, and composite Z score. Patients with mild tau and A β pathology also showed a significant improvement in steps to turn 180°. By contrast, patients with moderate-to-severe pathology did not show improvement on any study measure (Table 2).

Discussion

In this prospective study of patients who underwent shunting for iNPH, we found a high prevalence of AD pathology, comparable to that previously reported in similarly aged patients.¹⁶ Overall, patients in our cohort who underwent shunting for iNPH experienced improvements in gait, cognition, and bladder control. However, patients with moderate-to-severe tau and A β pathology demonstrated more severe baseline impairment on a composite measure of cognition and poorer performance postoperatively on NPH symptom severity scales and measures of cognition. Finally, in sharp contrast to individuals with less severe pathology, patients with moderate-to-severe pathology failed to demonstrate benefit on any study measures assessing gait, cognition, and incontinence at 4-month follow-up.

These findings are noteworthy in the context of prior studies in which the presence of AD pathology did not affect outcomes among patients shunted for iNPH. For example, Bech and colleagues³ found AD pathology in 6 of 27 patients treated for iNPH, and interestingly noted a tendency toward a higher improvement rate in patients with AD pathology. Golomb and colleagues⁴ found that cortical AD pathology in patients with iNPH correlated with dementia severity and gait impairment at presentation, but not with subsequent outcomes. Bech-Azeddine and colleagues⁵ found pathologically diagnosed AD in 7 (25%) of 28 patients and determined that the presence of clinical features of AD did not accurately predict response to shunting, but did not specifically evaluate the impact of cortical pathology on clinical outcome.

Several factors may have contributed to differences between the current and prior findings. The methods used to measure AD pathology have varied between studies. Bech and colleagues³ did not employ tau as a pathologic criterion; Golomb and colleagues⁴ used neuritic plaques as the sole measure of pathology. These and other technical issues, including antibodies, antigen retrieval methods, and the timing of biopsy during the onset and progression of iNPH, may account for a higher incidence of AD pathology in our cohort than that observed in prior similar investigations.^{4,17} Moreover, our finding that patients with mild pathology respond well to shunting is consistent with data indicating that some patients are relatively unimpaired by the presence of cortical AD pathology,¹⁸ and suggests that prior studies that used dichotomous distinctions between patients with and without AD may have obscured the performance of patients with more severe AD pathology by grouping them with milder cases.

One limitation of the study is that CSF dynamics, an important consideration in the diagnosis of iNPH, was not formally assessed.¹¹ However, there is no evidence to suggest that patients with or without AD pathology who present with clinical and radiographic features of iNPH would differ in this respect. Another limitation of this study is its relatively small sample size. If our data could be replicated in larger samples, they would suggest that measures of cortical tau and A β are potentially useful in predicting outcomes for patients being evaluated for iNPH. This is germane in the context of growing evidence that biological markers such as A β and tau derived from CSF may prove useful for signifying the presence of AD.¹⁹ Furthermore, techniques such as positron emission tomography imaging with ¹¹C-labeled Pittsburgh compound B—a compound retained in cortical regions that contain significant A β —also hold promise as tools for assessing the presence and progression of AD.²⁰ Given our finding that cortical tau and A β accumulations are associated with poorer outcomes, noninvasive techniques that identify the presence of AD pathology may potentially play an important future role in the evaluation of iNPH.

References

1. Malm J, Kristensen B, Stegmayr B, et al. Three-year survival and functional outcome of patients with idiopathic adult hydrocephalus syndrome. *Neurology* 2000;55:576–578. [PubMed: 10953197]
2. Agyok G, Marmarou A, Young HF. Three-year outcome of shunted idiopathic NPH patients. *Acta Neurochir Suppl* 2005;95:241–245. [PubMed: 16463857]
3. Bech RA, Waldemar G, Gjerris F, et al. Shunting effects in patients with idiopathic normal pressure hydrocephalus: correlation with cerebral and leptomeningeal biopsy findings. *Acta Neurochir (Wien)* 1999;141:633–639. [PubMed: 10929729]
4. Golomb J, Wisoff J, Miller DC, et al. Alzheimer's disease comorbidity in normal pressure hydrocephalus: prevalence and shunt response. *J Neurol Neurosurg Psychiatry* 2000;68:778–781. [PubMed: 10811706]
5. Bech-Azeddine R, Høgh P, Juhler M, et al. Idiopathic normal-pressure hydrocephalus: clinical comorbidity correlated with cerebral biopsy findings and outcome of cerebrospinal fluid shunting. *J Neurol Neurosurg Psychiatry* 2007;78:157–161. [PubMed: 17012342]

6. Poca MA, Mataró M, Del Mar Matarín M, et al. Is the placement of shunts in patients with idiopathic normal-pressure hydrocephalus worth the risk? Results of a study based on continuous monitoring of intracranial pressure. *J Neurosurg* 2004;100:855–866. [PubMed: 15137605]
7. Holden MK, Gill KM, Magliozzi MR, et al. Clinical gait assessment in the neurologically impaired: standards for outcome assessment. *Phys Ther* 1984;64:35–40. [PubMed: 6691052]
8. Beekly DL, Ramos EM, Lee WW, et al. The National Alzheimer's Coordinating Center (NACC) database: the Uniform Data Set. *Alzheimer Dis Assoc Disord* 2007;21:249–258. [PubMed: 17804958]
9. McBride T, Moberg PJ, Arnold SE, et al. Neuropsychological functioning in elderly patients with schizophrenia and Alzheimer's disease. *Schizophr Res* 2002;55:217–227. [PubMed: 12048145]
10. Evans WA. An encephalographic ratio for estimating ventricular and cerebral atrophy. *Arch Neurol Psych* 1942;47:931–937.
11. Marmarou A, Bergsneider M, Relkin N, et al. Development of guidelines for idiopathic normal-pressure hydrocephalus: introduction. *Neurosurgery* 2005;57:S1–S3. [PubMed: 16160424]
12. Lee EB, Skovronsky DM, Abtahian F, et al. Secretion and intracellular generation of truncated Abeta in beta-site amyloid-beta precursor protein-cleaving enzyme expressing human neurons. *J Biol Chem* 2003;278:4458–4466. [PubMed: 12480937]
13. Otvos L Jr, Feiner L, Lang E, et al. Monoclonal antibody PHF-1 recognizes tau protein phosphorylated at serine residues 396 and 404. *J Neurosci Res* 1994;39:669–673. [PubMed: 7534834]
14. Duda JE, Giasson BI, Mabon ME, et al. Novel antibodies to synuclein show abundant striatal pathology in Lewy body diseases. *Ann Neurol* 2002;52:205–210. [PubMed: 12210791]
15. Uryu K, Nakashima-Yasuda H, Forman MS, et al. Concomitant TAR-DNA-binding protein 43 pathology is present in Alzheimer's disease and corticobasal degeneration but not in other tauopathies. *J Neuropathol Exp Neurol* 2008;67:555–564. [PubMed: 18520774]
16. Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiol Aging* 1997;18:351–357. [PubMed: 9330961]
17. Del Bigio MR, Cardoso ER, Halliday WC. Neuropathological changes in chronic adult hydrocephalus: cortical biopsies and autopsy findings. *Can J Neurol Sci* 1997;24:121. [PubMed: 9164688]
18. Davis D, Schmitt F, Wekstein D, Markesbery W. Alzheimer neuropathologic alterations in aged cognitively normal subjects. *J Neuropathol Exp Neurol* 1999;58:376–388. [PubMed: 10218633]
19. Shaw LM, Vanderstichele H, Knapik-Czajka M, et al. Cerebrospinal fluid biomarker signature in Alzheimer's Disease Neuroimaging Initiative subjects. *Ann Neurol* 2009;65:403–413. [PubMed: 19296504]
20. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol* 2004;55:306–319. [PubMed: 14991808]

FIGURE 1.

Tau and amyloid β ($A\beta$) pathology in patients with idiopathic normal pressure hydrocephalus. Representative sections stained with PHF1 for tau pathology (left), thioflavin S for $A\beta$ pathology (middle), and NAB228 for $A\beta$ pathology (right) are shown (original magnification, $\times 200$). Some cases demonstrated rare (0.5+) (A) to mild (1+) (B) tau pathology, with 1 case showing predominantly astrocytic tau pathology (C). Thioflavin S staining demonstrated select cases with mild (1+) (D) to moderate (2+) (E) neuritic plaque burden. Thioflavin S stain also demonstrated cases with neurofibrillary tangles (NFT) (F) and/or $A\beta$ angiopathy (G). Since tau tangles were rare, they were sometimes seen only on 1 level (either PHF1-stained section or thioflavin S-stained section), although if present they were usually seen with both stains. NAB228 highlighted $A\beta$ positive plaques, and cases ranging from mild (1+) to severe (3+) are shown (H–J).

FIGURE 2.

Performance of subjects before and after surgery on study measures stratified by degree of cortical pathology. Error bars indicate standard error. (A) Performance on a 15-point normal pressure hydrocephalus (NPH) scale comprised of 3 5-point subscales assessing gait, incontinence, and cognition as a whole cohort and stratified according to the presence of no pathology, mild pathology, or moderate-to-severe pathology. (B) Change in performance on the composite Z score of cognitive measures as a whole cohort and stratified according to the presence of no pathology, mild pathology, or moderate-to-severe pathology.

TABLE 1

Prevalence and Severity of Cortical Pathology (N=37)

Pathology	Absent	Rare	Low	Moderate	High
Aβ plaques	12 (32.4%)	0 (0%)	6 (16.2%)	12 (32.4%)	7 (18.9%)
Neuritic plaques	14 (37.8%)	0 (0%)	9 (24.3%)	14 (37.8%)	0 (0%)
Tau	27 (73.0%)	4 (10.8%)	6 (16.2%)	0 (0%)	0 (0%)

Aβ = amyloid β.

Change in Performance from Baseline to Follow-up for No Pathology, Mild Pathology, and Moderate-to-Severe Pathology Groups (Paired *t* Tests)

TABLE 2

Characteristic	No Pathology	Mild Pathology	Moderate-Severe Pathology						
No.	8	14	8						
Mean Age (yr)	73.5	73.6	78.4						
Education (yr)	14.8	14.1	13.1						
Gender (M/F)	6/2	9/5	2/6						
	Mean Difference	<i>t</i>	<i>p</i>	Mean Difference	<i>t</i>	<i>p</i>			
NPH scale total	3.13	4.69	0.0022	2.43	8.34	<0001	0.38	0.57	0.5837
Gait	1.25	5.00	0.0016	1.00	6.75	<0001	0.13	0.55	0.5983
Cognitive	0.88	2.97	0.0209	0.50	3.61	0.0032	0.00	0.00	1.0000
Incontinence	1.25	3.99	0.0053	1.00	4.42	0.0008	0.25	0.80	0.4512
Percent change gait time	-32.05	4.37	0.0033	-24.98	3.66	0.0033	2.40	0.14	0.8913
Quality of gait	-0.75	3.00	0.0199	-0.64	3.23	0.0066	0.00	0.00	1.0000
Steps to turn 180°	-0.75	0.63	0.5490	-1.69	3.16	0.0082	0.63	0.40	0.7043
Composite Z score	0.49	2.81	0.0307	0.39	4.49	0.0015	-0.06	0.48	0.6627

NPH = normal pressure hydrocephalus.