Association between shunt-responsive idiopathic normal pressure hydrocephalus and alcohol

*Thu-Trang Hickman, MPH,¹ Matthew E. Shuman, BA,¹ Tatyana A. Johnson,¹ Felix Yang, BS,¹ Rebecca R. Rice,¹ Isaac M. Rice,¹ Esther H. Chung, BA,¹ Robert Wiemann, BA,¹ Megan Tini, DPT,^{1,2} Christine Iracheta, PT,^{1,2} Grace Chen, DPT,^{1,2} Patricia Flynn, PT,^{1,2} Mary Beth Mondello, NP, MSN,¹ Jillian Thompson,¹ Mary-Ellen Meadows, PhD,^{1,3} Rona S. Carroll, PhD,¹ Hong Wei Yang, MD, PhD,¹ Hongyan Xing, PhD,¹ David Pilgrim, MD,^{1,3} E. Antonio Chiocca, MD, PhD,¹ Ian F. Dunn, MD,¹ Alexandra J. Golby, MD,¹ and Mark D. Johnson, MD, PhD¹

¹Adult Hydrocephalus Program, Department of Neurosurgery, Brigham and Women's Hospital and Harvard Medical School;

²Department of Rehabilitation Services, Brigham and Women's Hospital; and ³Department of Neurology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

OBJECTIVE Idiopathic normal pressure hydrocephalus (iNPH) is characterized by ventriculomegaly, gait difficulty, incontinence, and dementia. The symptoms can be ameliorated by CSF drainage. The object of this study was to identify factors associated with shunt-responsive iNPH.

METHODS The authors reviewed the medical records of 529 patients who underwent shunt placement for iNPH at their institution between July 2001 and March 2015. Variables associated with shunt-responsive iNPH were identified using bivariate and multivariate analyses. Detailed alcohol consumption information was obtained for 328 patients and was used to examine the relationship between alcohol and shunt-responsive iNPH. A computerized patient registry from 2 academic medical centers was queried to determine the prevalence of alcohol abuse among 1665 iNPH patients.

RESULTS Bivariate analysis identified associations between shunt-responsive iNPH and gait difficulty (OR 4.59, 95% CI 2.32–9.09; $p < 0.0001$), dementia (OR 1.79, 95% CI 1.14–2.80; $p = 0.01$), incontinence (OR 1.77, 95% CI 1.13–2.76; $p = 0.01$), and alcohol use (OR 1.98, 95% CI 1.23–3.16; $p = 0.03$). Borderline significance was observed for hyperlipidemia (OR 1.56, 95% CI 0.99–2.45; $p = 0.054$), a family history of hyperlipidemia (OR 3.09, 95% CI 0.93–10.26, $p = 0.054$), and diabetes (OR 1.83, 95% CI 0.96–3.51; $p = 0.064$). Multivariate analysis identified associations with gait difficulty (OR 3.98, 95% CI 1.81–8.77; $p = 0.0006$) and alcohol (OR 1.94, 95% CI 1.10–3.39; $p = 0.04$). Increased alcohol intake correlated with greater improvement after CSF drainage. Alcohol abuse was 2.5 times more prevalent among iNPH patients than matched controls.

CONCLUSIONS Alcohol consumption is associated with the development of shunt-responsive iNPH.

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KEY WORDS normal pressure hydrocephalus; gait disorders; incontinence; cognitive impairment; aging; alcohol

IDIOPATHIC normal pressure hydrocephalus (iNPH) is a neurological disorder that is characterized by gait instability, dementia, and urinary incontinence.^{1,15} Imaging findings include enlarged cerebral ventricles, deep white matter or periventricular white matter abnormalities, and alterations in the size of the subarachnoid spaces.⁴⁰ It has been estimated that about 1.4% of patients older than 65 years and up to 14% of patients in nursing homes have iNPH, most of whom are undiagnosed.^{6,20,27,36} Because placement of a shunt to drain the CSF can improve the symptoms,^{14,22,37} iNPH has been classified as one of the reversible dementias.

The etiology of shunt-responsive iNPH is unknown. However, clinical studies of iNPH have led to multiple hypotheses regarding its origins. Abnormalities of the cerebral vasculature and defects in CSF circulation are among the leading candidates. In support of the vascular hypothesis, several studies have reported an increased association of vascular risk factors with shunt-responsive iNPH.^{7,9,11,16,18,21,23,24,33,34} Hypertension, diabetes, and cardiac disease have all been associated with shunt-responsive iNPH.²⁴ Periventricular and deep white matter lesions are often seen on MRI in patients with shunt-responsive iNPH and are thought by many to represent cerebral small vessel dis-

ABBREVIATIONS iNPH = idiopathic normal pressure hydrocephalus; TUG = Timed Up and Go.

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* Mrs. Hickman and Mr. Shuman contributed equally to this work.

ease.⁴⁰ In fact, patients with Binswanger's cerebrovascular encephalopathy can improve after CSF drainage.^{33,37}

Disorders of CSF absorption have also been postulated as causes of shunt-responsive iNPH. Perhaps the strongest evidence in favor of this hypothesis is that ventricular enlargement is a hallmark of shunt-responsive iNPH, and CSF drainage improves the symptoms.^{1,14,15,22,37,40} In addition, studies have suggested the presence of impaired CSF circulation and abnormal subarachnoid spaces in shunt-responsive iNPH patients, providing additional support for the CSF hypothesis.³

It is unclear whether behavioral or environmental factors contribute to the development of shunt-responsive iNPH. Here, we report a correlation between the development of shunt-responsive iNPH and increased alcohol consumption.

Methods

Study Design and Data Collection

The study was conducted under the auspices of a human subjects research protocol approved by the Partners Institutional Review Board Committee. We retrospectively reviewed the medical records of patients diagnosed with disorders of CSF flow at Brigham and Women's Hospital between July 2001 and May 2015 to identify patients who had undergone evaluation for iNPH. Patients were selected for evaluation of possible iNPH if they were found to have communicating hydrocephalus on CT or MR images, gait disturbance, urinary urgency/incontinence, cognitive impairment, and no clearly identifiable cause of their symptoms. At the time of the first clinic visit, clinical and demographic data were collected using a patient questionnaire. We combined these prospectively collected data with additional information retrieved from an electronic medical record.

We also identified patients for whom detailed information on the amount of alcohol consumed was available. Using dietary recommendations published by the US Department of Health and Human Services and the US Department of Agriculture as a guide,³⁹ we divided alcohol consumption into 4 categories: never (abstinence), rare/occasional (3 alcoholic beverages or fewer weekly), moderate (4–14 alcoholic beverages weekly) and heavy (more than 14 alcoholic beverages weekly). A guideline that takes into account the lower threshold for heavy drinking among women of more than 1 drink/day was also used.³⁹

To determine the prevalence of alcohol abuse among a larger iNPH cohort, we queried a computerized, diagnostic code-based patient registry (Partners Healthcare System Research Patient Data Registry). The query, which was performed in February 2015, searched the medical records of 3,853,907 patients from 2 large academic medical centers (Brigham and Women's Hospital and Massachusetts General Hospital) using the diagnostic codes for iNPH and alcohol abuse not otherwise specified. A control group matched for age, sex, and race was assembled for comparison.

Outcome Assessment

Patients were evaluated by a group of board-certified

neurosurgeons and/or neurologists before and after CSF drainage trials and shunt placement. Quantitative and qualitative assessments of Timed Up and Go (TUG) tests, Tinetti balance tests, and other evaluations of gait and balance were performed by physical therapists during a 3-day CSF drainage trial. Additional information regarding changes in gait, cognition, and urinary or fecal continence was obtained from patient and caregiver reports.

Patients who showed signs of improvement in gait, incontinence, or cognition after a trial of CSF drainage were offered ventriculoperitoneal shunt placement. Patients were evaluated postoperatively at 2 weeks and at 6 weeks, and were then followed with periodic monthly or annual clinic visits as needed for a period of up to 11 years. Changes in gait were based on assessments of TUG time, gait speed, step height, cadence, balance, the need for gait assistive devices, and the number of falls. Changes in urinary/fecal incontinence or urgency were assessed in collaboration with nursing staff, caregivers, and patients. Urinary and fecal incontinence were assessed via written questionnaire and via daily inquiries of nursing staff, patients, and caregivers during the extended trial of lumbar CSF drainage and during preoperative and postoperative clinic visits. Changes in cognitive function were assessed using neurological examinations, formal neurocognitive evaluations (including the Montreal Cognitive Assessment, Mini-Mental State Examination, and evaluations by a licensed cognitive psychologist), statements by caregivers, and patient self-reports. These criteria were collectively used to categorize the degree of improvement within 1 year of shunt placement as markedly improved, mildly improved, or not improved. The combined criteria for not improved were 1) no improvement in ambulation; 2) no improvement in gait speed or TUG time; 3) no decrease in the number of falls; 4) no improvement in incontinence or urgency; 5) no improvement in the need for assistance with activities of daily living; 6) no improvement in reasoning, cognitive, or conversational abilities; and 7) no improvement in memory. The combined criteria for mild improvement were 1) progression from the use of one gait assistive device to a lesser device; 2) less than a 10% improvement in gait speed or TUG time; 3) a decrease in the number of falls; 4) less than a 50% decrease in episodes of incontinence or urgency; 5) decreased need for assistance with activities of daily living, but no change in independence; 6) mild improvement in reasoning, cognitive, or conversational abilities; and 7) mild improvement in memory. The combined criteria for marked improvement were 1) progression to ambulation without assistance; 2) greater than a 10% improvement in gait speed or TUG time; 3) complete cessation of falls; 4) greater than a 50% decrease in episodes of incontinence or urgency; 5) progression from dependent to assisted living, or from assisted to independent living; 6) marked improvement in reasoning, cognitive, or conversational abilities; and 7) marked improvement in memory.

Ventriculoperitoneal Shunt Surgery

Patients for whom a trial of CSF drainage supported a diagnosis of probable iNPH underwent surgical implantation of a ventriculoperitoneal shunt as treatment for their

FIG. 1. Study design. Flow diagram depicting the design for the iNPH study.

symptoms. The shunts generally contained programmable valves (Codman, Inc.) programmed initially to a setting of 120 mm H₂O. Valve settings were adjusted postoperatively as needed to maximize symptom improvement and minimize signs or symptoms of overdrainage, such as positional headaches or subdural hematomas.

Statistical Analysis

For statistical analysis, we used the SAS statistical software program (version 9.3, SAS Institute). Bivariate analysis was used to determine whether there were significant differences in presenting symptoms or the presence of clinical or demographic factors between patients who improved after shunt placement and those who did not improve. For medical history or family history variables, the presence or absence of disease documentation in the medical record was used to categorize patients as affected or unaffected, respectively. Consistent with clinical practice, medical history or family history variables were treated as binary and were marked as positive only when they were found in the patients' medical records. For analysis of tobacco or alcohol use, patients were divided into users, nonusers, and those for whom no information was available. The chi-square test of homogeneity was used to determine statistical significance, and $p \leq 0.05$ was set as the threshold. A multivariate logistic regression analysis

was used to investigate the association between the variables considered and improvement after shunt placement. The independent predictor variables included presenting clinical symptoms, medical history, family history, tobacco and alcohol use, age, and sex. Statistical significance was set at the $p \leq 0.05$ level.

For the analysis of data regarding the prevalence of alcohol use among patients with iNPH, statistical significance was determined using the proportion test. A z-score was calculated based on a 2-tailed hypothesis, and significance was set at $p \leq 0.05$. All statistical analyses were performed by 2 authors (T.T.H. and M.J.).

Results

Patient Population

We identified 622 patients who presented with clinical symptoms and imaging findings consistent with iNPH. After an evaluation that included history taking, neurological examination, cranial imaging, and a trial of CSF drainage, 529 patients (267 men and 262 women) were suspected to have iNPH and underwent shunt placement (Fig. 1). The median and mean duration of symptoms prior to evaluation for iNPH were 24 months and 29.6 ± 20.9 months (mean $\pm$ SD), respectively. More than 95% of the patients who underwent shunt placement presented with

gait difficulty as one of their primary symptoms. About 63% of patients had the classic iNPH symptom triad of gait difficulty, urinary incontinence/urgency, and cognitive impairment.

The mean follow-up duration after shunt placement was 32.3 ± 30.8 months, with a range of 1–132 months (median 22 months). Of the 529 patients who underwent shunt placement, 418 (79%) improved (shunt-responsive iNPH group) and 111 (21%) did not improve (not shunt-responsive iNPH group). Approximately 78% of patients who presented with the iNPH symptom triad improved after shunt placement. Patients who presented with gait difficulty alone (8%) or in combination with either incontinence (11%) or cognitive deficits (17%) improved about 60% of the time after CSF drainage. Demographic and clinical characteristics of the patients who improved after shunt placement and those who did not are shown in Table 1.

Factors Associated With Shunt-Responsive iNPH

Bivariate analysis identified several factors that are associated with the presence of shunt-responsive iNPH (Fig. 2). Presenting symptoms associated with shunt-responsive iNPH included gait difficulty (OR 4.59, CI 2.32–9.09; $p < 0.0001$), cognitive dysfunction (OR 1.79, CI 1.14–2.80; $p = 0.01$) and urinary urgency/incontinence (OR 1.77, CI 1.13–2.76; $p = 0.01$). Among comorbid conditions, positive trends toward significance were observed for hyperlipidemia (OR 1.56, CI 0.99–2.45; $p = 0.054$) and diabetes (OR 1.83, CI 0.96–3.51; $p = 0.064$). In addition, a positive trend toward significance was seen for a family history of hyperlipidemia (OR 3.09, CI 0.93–10.26; $p = 0.054$). A positive association between alcohol use and the presence of shunt-responsive iNPH was also observed (OR 1.97, CI 1.23–3.16; $p < 0.03$). We did not observe significant associations between iNPH and hypertension (OR 1.23, CI 0.79–1.90; $p = 0.36$) or smoking (OR 0.99, CI 0.62–1.56; $p = 0.95$).

For multivariate analysis, we used a more parsimonious model containing 15 variables (Fig. 3). This analysis identified positive associations between the presence of shunt-responsive iNPH and gait difficulty (OR 3.98, CI 1.81–8.77; $p < 0.0006$) or alcohol consumption (OR 1.94, 95% CI 1.10–3.39; $p = 0.04$).

Alcohol and Shunt-Responsive iNPH

We performed further analysis of 328 patients (162 men and 166 women) for whom detailed information regarding the amount of alcohol consumed was available. Overall, 47% of these patients consumed alcohol to some degree. This prevalence was comparable to the prevalence of alcohol use of 46% observed among a group of 152 brain tumor patients 60 years and older identified at our institution. However, 54% of patients who improved after CSF drainage consumed alcohol, while only 26% of those who did not improve consumed alcohol (z -score = -3.94 , $p < 0.0001$).

A positive relationship between increased alcohol consumption and the probability of having shunt-responsive iNPH was observed. After CSF drainage, approximately 63% of nondrinkers improved, 82% of rare/occasional drinkers improved, 87% of moderate drinkers improved,

TABLE 1. Characteristics of groups stratified by outcome after shunt placement for iNPH

Characteristic	Improved	Not Improved
Mean age, yrs $\pm$ SD	74.7 $\pm$ 7.3	74.6 $\pm$ 7.4
Male sex	212 (50.7%)	55 (49.6%)
Gait instability	400 (95.7%)	92 (82.9%)
Cognitive difficulty	318 (76.1%)	71 (64.0%)
Urinary urgency/incontinence	314 (75.1%)	70 (63.1%)
Headache	15 (3.6%)	3 (2.7%)
Hypertension	283 (67.7%)	70 (63.1%)
Cardiac disease	69 (16.5%)	20 (18.0%)
Arthritis	56 (13.4%)	12 (10.8%)
Inflammatory disease	81 (19.4%)	20 (18.0%)
Renal disease	26 (6.2%)	5 (4.5%)
Asthma	27 (6.5%)	4 (3.6%)
Diabetes	76 (18.2%)	12 (10.8%)
Hypothyroidism	45 (10.8%)	10 (9.0%)
Hyperthyroidism	8 (1.9%)	1 (0.9%)
All thyroid disease	66 (15.8%)	13 (11.7%)
Trauma	3 (0.7%)	1 (0.9%)
Cancer	92 (22.0%)	21 (18.9%)
Fracture	10 (2.4%)	1 (0.9%)
Hyperlipidemia	166 (39.7%)	33 (29.7%)
Family Hx of cancer	77 (18.4%)	18 (16.2%)
Family Hx of Alzheimer's disease	11 (2.6%)	3 (2.7%)
Family Hx of Parkinson's disease	11 (2.6%)	3 (2.7%)
Family Hx of hypertension	58 (13.9%)	10 (9.0%)
Family Hx of stroke	16 (3.8%)	3 (2.7%)
Family Hx of hyperlipidemia	33 (7.9%)	3 (2.7%)
Family Hx of cardiac disease	73 (17.5%)	20 (18.0%)
Family Hx of renal disease	1 (0.2%)	1 (0.9%)
Family Hx of asthma	3 (0.7%)	0 (0.0%)
Family Hx of dementia	16 (3.8%)	6 (5.4%)
Family Hx of gait difficulty	1 (0.2%)	1 (0.9%)
Smoking	123 (29.4%)	33 (29.7%)
Alcohol use	166 (39.7%)	30 (27.0%)
Recreational drug use	3 (0.7%)	1 (0.9%)

Hx = history.

and 90% of heavy drinkers improved (z -score = -2.57 , $p < 0.01$; Fig. 4A). The mean age for drinkers (74.7 ± 7.3 years) and nondrinkers (73.7 ± 8.6 years) was not significantly different. However, the female to male ratio was 1:1.7 for drinkers and 0.83:1 for nondrinkers, consistent with studies demonstrating a higher prevalence of alcohol use among men.¹⁹ When the data for men and women were analyzed separately using sex-specific guidelines for heavy drinking (i.e., more than 1 drink daily for women and 2 drinks daily for men), a positive relationship between increased alcohol consumption and the probability of having shunt-responsive iNPH was seen for both men and women (Fig. 4B).

At the time of database construction and prior to statistical analysis, patient responses after shunt placement were

FIG. 2. Univariate analysis of variables associated with shunt-responsive iNPH. Data shown are odds ratios and 95% confidence intervals; p values were calculated using the chi-square test. Hx = history. Figure is available in color online only.

categorized as no improvement, mild improvement, or marked improvement using the criteria outlined in *Methods*. We observed that the prevalence of alcohol use increased as the level of improvement after shunt placement increased (Fig. 4C and D). Importantly, a dose-dependent relationship between the amount of alcohol consumed and the level of improvement observed after shunt placement was seen for both men and women (Fig. 4E).

Hospital-Based Computer Registry Analysis

To examine the prevalence of hypertension and alcohol use among a larger group of iNPH patients, we queried a hospital-based computer registry of more than 3.8 million patients from our institution and a second large academic medical center, Massachusetts General Hospital. Using the registry, we identified 1665 patients with a diagnosis of iNPH. A control group of 1661 patients matched for age, sex, and race was also assembled. A query using the diagnosis “alcohol abuse NOS” identified 105,188 affected patients. Cross-referencing these groups identified 86

iNPH patients with a diagnosis of alcohol abuse but only 35 control group patients with this diagnosis (z-score = 4.7096, $p < 0.0001$).

For comparison, we conducted additional queries to investigate the prevalence among iNPH patients of acute appendicitis and toothache, 2 diagnoses that we hypothesized to be unrelated to iNPH. Approximately 15,387 patients with a diagnosis of acute appendicitis were identified in the registry, and 21,105 patients with a diagnosis of toothache were similarly identified. There was no statistically significant difference in the number of iNPH patients or matched control group patients diagnosed with acute appendicitis (8 patients in each group, $p < 1.0$) or toothache ($n = 11$ for iNPH, $n = 5$ for control group; z-score = 1.5, $p < 0.13$).

Discussion

Cardiovascular Risk Factors and Shunt-Responsive iNPH

Previous investigators have reported associations be-

FIG. 3. Multivariate analysis of variables associated with shunt-responsive iNPH. Data shown are odds ratios and 95% confidence intervals. $Pr > \chi^2$ indicates that chi-square values were obtained using logistic regression analysis. Figure is available in color online only.

tween iNPH and cardiovascular risk factors, such as hypertension, hyperlipidemia, and diabetes.^{7,9,11,16,18,21,23,24,33,34}

In the current study, bivariate analysis revealed strong positive trends toward significance for hyperlipidemia ($p = 0.054$), a family history of hyperlipidemia ($p = 0.054$), and diabetes ($p = 0.064$). The mechanisms underlying the association between cardiovascular risk factors and shunt-responsive iNPH are not known. One possibility is that hyperlipidemia, diabetes, or other cardiovascular risk factors promote cerebrovascular disease and decreased cerebral blood flow in the deep white matter, and this leads to cognitive and motor dysfunction. Imaging studies have identified microvascular abnormalities in the deep white matter and periventricular areas of the brain in a subpopulation of patients with iNPH.^{9,18,22,23,25,33,34,40} Cerebral blood flow studies have documented decreased cerebral blood flow and decreased cerebrovascular reactivity in iNPH patients, raising the possibility that iNPH is a disease of the cerebral vasculature. Interestingly, some studies have indicated that cerebral blood flow increases and deep white matter lesions decrease in iNPH patients after shunt placement,^{2,8,29} although others have disputed these findings.²⁵

Diabetes and hyperlipidemia promote atherosclerosis and have been postulated to play a causal role in mild cognitive impairment.⁴ Arteriosclerotic changes have been identified in postmortem studies of patients with iNPH in about 60% of cases.²⁶ Interestingly, patients with Binswanger's disease (hypertension with subcortical arteriosclerotic disease and dementia) can improve after shunt placement.³⁷

The fact that hyperlipidemia and diabetes have been associated with iNPH in multiple studies raises the possibility that abnormal lipid metabolism or cerebrovascular disease may contribute to this disorder.

Alcohol Consumption and Shunt-Responsive iNPH

Here, we present the first evidence for a robust association between an exposure (alcohol use) and the presence of shunt-responsive iNPH. Even rare alcohol consumption was associated with an increased likelihood of having shunt-responsive iNPH. Moreover, increasing levels of alcohol consumption were associated with increasing degrees of improvement after shunt placement.

It is not possible from this study to infer a causal relationship between alcohol use and the development of shunt-responsive iNPH. In fact, these data are consistent with at least 2 very different hypotheses. One hypothesis is that alcohol use increases the response to CSF drainage in patients who have iNPH. Cerebral blood flow and cerebrovascular reactivity are impaired in iNPH patients, and both are reportedly increased after CSF drainage in patients who improve.^{2,8,29} Alcohol has vasoactive properties,⁵ and numerous studies have shown that alcohol increases cerebral blood flow in a dose-dependent manner.^{17,35,38} Thus, it is tempting to speculate that alcohol enhances the ability of CSF drainage to increase cerebral blood flow, and that this promotes improved outcomes after shunt placement.

An alternative hypothesis, however, is that alcohol promotes the development of shunt-responsive iNPH. In addition to Wernicke-Korsakoff syndrome, heavy alcohol use

FIG. 4. **A:** Percentage of patients who improved (red bars) or did not improve (blue bars) after shunt placement for iNPH, grouped according to amount of alcohol consumed. The number of patients involved in each category is shown at the top of each column. Criteria for classifying the frequency of alcohol consumption were as follows: never (abstinence), rare (3 alcoholic beverages or less weekly), moderate (4–14 alcoholic beverages weekly), and heavy (more than 14 alcoholic beverages weekly). **B:** Percentage of men and women who improved (red bars) or did not improve (blue bars) after shunt placement for iNPH, grouped according to frequency of alcohol consumption. Criteria for classifying the frequency of alcohol consumption for men were the same as in panel A. Criteria for classifying the frequency of alcohol consumption for women were never (abstinence), moderate (up to 7 alcoholic beverages weekly), and heavy (more than 7 alcoholic beverages weekly). **C:** Prevalence of drinkers among patients showing no improvement (none), mild improvement, or marked improvement after CSF drainage for iNPH. The number of patients in each category is shown at the top of each column. **D:** Graph illustrating relationship between the degree of improvement after CSF drainage for iNPH and the frequency of alcohol consumption. **E:** Graph showing the relationship between the number of drinks consumed weekly and the degree of improvement for men and women.

can produce alcohol-related dementia.³² Alcohol causes injury to cerebral vessels and damage to the deep white matter of the brain, which increases with age.^{12,13,31} Alcohol also disrupts the blood-CSF barrier³⁰ and the blood-brain barrier,¹⁰ and it decreases cognitive function in animals.¹⁰ Recent studies in humans have shown that defects in the blood-brain barrier arise during aging and correlate with mild cognitive impairment.²⁸ Thus, alcohol-mediated brain injury could act in concert with other aging-related processes to promote the development of shunt-responsive iNPH. Because iNPH is currently identified in part by the positive response to CSF drainage, differentiation between whether alcohol augments the treatment of shunt-responsive iNPH or promotes development of the disease itself will require elucidation of the underlying cause of this disorder.

Selection bias or information bias can adversely affect the interpretation of retrospective studies. In the current study, the selection of patients with iNPH, assessments

of the degree of improvement, and the amount of alcohol consumed were all documented prior to initiation of the study. No post hoc diagnoses or assessments were made, and all patients undergoing evaluation for iNPH during the study period were included. This significantly reduces (but does not eliminate) the potential for selection bias.

The retrospective nature of this study prevented us from rigorously controlling outcome assessment or alcohol exposure, and it necessitated that we rely instead on accurate recordkeeping by a number of health care providers during past patient encounters. Even with the large sample size of this study, inaccuracies in recording clinical comorbidities, exposures, or outcomes may have limited our ability to accurately identify associations between iNPH and other variables. In addition, recall bias may derive from inaccuracies in patient reporting of alcohol consumption. Because patients may not have been forthcoming about alcohol use, nonreporting or underreporting of alcohol consumption could minimize the apparent differences in

iNPH prevalence and outcomes between alcohol users and nonusers in this study.

Conclusions

The findings reported here reveal an association between alcohol and the development of shunt-responsive iNPH. Previous associations with cardiovascular risk factors, such as diabetes, hyperlipidemia, and hypertension were also identified. The consumption of alcohol is the first exposure associated with shunt-responsive iNPH, and it joins existing associations with cardiovascular risk factors found in this and in previous studies. Accumulating reports indicate that the development of many neurological disorders of aging (e.g., Alzheimer's disease, Parkinson's disease, hearing loss, and mild cognitive impairment) can be influenced by behavior or by environmental exposures. Our study indicates that this may be true for iNPH as well. Prospective studies designed to determine whether alcohol consumption promotes the development of iNPH or, alternatively, whether it increases the response to CSF drainage in patients who already have the disease, should be conducted. The interpretation of such studies would be aided by the discovery of the underlying causes and elucidation of the pathophysiology of iNPH.

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Disclosures

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Author Contributions

Conception and design: Johnson. Acquisition of data: Johnson, Hickman, Shuman, Johnson, F Yang, RR Rice, IM Rice, Chung, Wiemann, Tinkl, Iracheta, Chen, Flynn, Mondello, Thompson, Carroll, HW Yang, Pilgrim, Chiocca, Dunn, Golby. Analysis and interpretation of data: Johnson, Hickman, Shuman, Tinkl, Iracheta, Chen, Flynn. Drafting the article: Johnson, Hickman, Shuman. Critically revising the article: Johnson, Hickman, Shuman. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Johnson. Statistical analysis: Johnson, Hickman, Shuman. Administrative/technical/material support: Johnson. Study supervision: Johnson.

Correspondence

Mark D. Johnson, Department of Neurosurgery, Harvard Medical School, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115. email: mjohnson27@partners.org.