First identified in 1965, idiopathic normal pressure hydrocephalus (iNPH) is a syndrome of progressive neurological deterioration associated with ventricular enlargement but normal cerebrospinal fluid (CSF) pressure on lumbar puncture. Classically, the disease has been associated with a syndromic triad of gait disturbance, urinary incontinence, and cognitive decline, with gait disturbance and one other feature generally required for diagnosis. Generally, the diagnosis of iNPH is multifactorial and made through the assessment of clinical symptoms, imaging, CSF pressure measurements, and response to CSF drainage. Although the pathology underlying these cases is still unknown, iNPH remains one of the few causes of dementia and cognitive decline that is potentially reversible.

The standard treatment for iNPH is surgical CSF diversion, most commonly through implantation of a ventriculoperitoneal (VP) shunt, to alleviate the clinical symptoms associated with the disease.
caused by excess intracranial fluid. The rate of successful shunt response in the treatment of iNPH has increased over the years. A 2001 meta-analysis of outcomes reported the treatment to have a 29% rate of significant improvement and a 6% significant complication rate. More recent studies have revealed greater improvements, with 75% of patients (n = 132) seeing postoperative improvements within 24 months of surgery in a retrospective study. Similarly, a smaller prospective study involving 33 patients with iNPH found that those in whom surgical treatment was delayed for more than 3 months had significantly poorer final outcomes as evaluated by the modified Rankin Scale. However, the study attributed the worse outcomes to neurological deterioration prior to surgery, as the magnitude of change with surgery was comparable to that in patients without treatment delay.

Not all studies have resulted in the conclusion that delaying treatment ultimately leads to worse iNPH outcomes. The findings of one study suggested that worse outcomes observed in patients with delayed treatment may actually be a function of delayed response to treatment. In the open-label randomized trial of 93 patients undergoing lumbar-peritoneal surgery for iNPH, patients who had surgery postponed for 3 months had worse outcomes at 3 months after surgery compared with those who received surgery within 1 month of study enrollment: 65% in the immediate treatment group versus 5% in the postponed treatment group saw an improvement of 1 point or more on the modified Rankin Scale. However, by 1 year after surgery, the difference in outcomes between the groups narrowed: 67% in the immediate treatment group versus 58% in the postponed treatment group saw an improvement of 1 point or more on the modified Rankin Scale. In another retrospective study involving 92 patients, improvement after CSF shunting did not exhibit any dependency on duration of symptoms.

Therefore, the extent and ways in which delayed treatment influences postoperative clinical outcomes remain to be elucidated. Given a prevalence of as much as 1.4% in the elderly adult population and 9%–14% in the assisted-living population, it is important to determine to what degree more aggressive identification of iNPH cases for early intervention may prevent morbidity and mortality. The objective of this study was to provide more clarity to these questions and to determine whether the duration of preoperative symptoms alters postoperative outcomes in patients treated for iNPH.

Methods

After approval was obtained from our institutional review board, a retrospective review was performed. All patients diagnosed with communicating idiopathic hydrocephalus and treated with VP shunts by the senior author (D.R.) at the Johns Hopkins Hospital between 1993 and 2013 were analyzed. Idiopathic NPH was diagnosed using standard clinical guidelines. Specifically, to more objectively identify patients with iNPH, the diagnosis was made by having at least 1 of the 3 cardinal iNPH symptoms of urinary incontinence, gait instability, and cognitive decline (with primarily at least gait instability) that improved following CSF removal during lumbar puncture (LP) and/or lumbar drainage trials, with opening pressure of all included patients being less than 25 cm H₂O. All patients underwent a CSF drainage trial prior to shunt placement. Additionally, the patients had normal morphology of the third ventricle on CT and/or MRI to exclude an obstructive etiology. Per diagnostic guidelines, patients younger than 40 years were excluded. Those with NPH after tumor surgery or NPH secondary to trauma or infection were also excluded.

Demographic information including baseline symptoms, age, sex, and race were recorded. In addition to clinical presentation, multiple markers were used to assess patient outcomes at six months following surgery and at last follow-up: MMSE, the modified Rankin Scale, the Barthel Index of Activities of Daily Living, the Wijkelsø score, the Timed Up-and-Go test, and the Tinetti balance assessment. Based on these results and subjective physician-documented assessments of clinical presentation, categorical changes in gait, urinary incontinence, and cognitive outcomes were also recorded 6 months following surgery and at last follow-up. Symptom changes were categorized as improvement, regression, or no change. An additional analysis was performed stratifying the patients by decade of age (40–50 years, 50–60 years, 60–70 years, 70–80 years, and 80+ years).

Statistics

Data analysis was performed using Stata 12 (StataCorp, College Station, Texas, USA). Multinomial logistic regression was used to determine the relationship between duration of symptoms prior to surgery and improvement in symptoms. Simple linear regression was used to determine the relationship between duration of symptoms and performance on objective clinical studies. Multivariate models compared symptom improvement with age, sex, race, and prior treatment as well. All reported p values were 2-sided and statistical significance was set at p < 0.05.

Results

A total of 393 patients were identified who met the criteria for inclusion in the study. Their median age at treatment was 74 years; 85% of patients were 65 years or older, 6% were between 60 and 65 years of age, and 9% were between ages 40 and 60 years of age. Patients predominantly presented with gait disturbance along with urinary incontinence and/or cognitive decline. In the series, 96.7% of the patients had gait disturbance, 85.5% presented with cognitive decline, and 88.0% presented with urinary inconti-
Additional, the baseline symptomatology was similar among patients with different symptom durations (Figs. 1–5). The median preoperative duration of symptoms was 28 months, the median follow-up duration was 31 months, and the median preoperative Evans index was 0.367 (Table 1). Of all measured outcomes, statistically significant associations with preoperative symptom duration were observed among categorical clinical outcomes. Trend were observed between increased symptom duration increasing the risk of having no 6-month postoperative improvement in urinary incontinence (RR 1.049 per year, p = 0.069) or cognitive symptoms (RR 1.051 per year, p = 0.069). However, when results were stratified by decade, a significant association was seen between symptom duration and risk of having no 6-month postoperative improvement in cognition (RR 1.121 per year, p = 0.027) among patients 70–80 years of age.

No statistical significance was noted with any of these assessments at last follow-up, and no other variables, including age, sex, race, or prior treatment substantially contributed in a multivariate model. Additionally, no statistically significant associations were found between preoperative symptom duration and any quantitative measurements of outcome such as the MMSE, the modified Rankin Scale, the Barthel Index, the Wikkelsø score, the Timed Up-and-Go test, and the Tinetti balance assessment. Decreased statistical power was seen with these analyses, as not all patients had all of the assessments due to evolutions.
in medical practice. However, when results were strati-
fied by decade, there was a significant association between
prolonged symptom duration and lower MMSE scores. For patients between 60–70 years of age, each month of
symptoms was associated with a decrease of 0.101 point in
MMSE score improvement 6 months postoperatively (R² =
0.194, F(1,24) = 4.83, p = 0.040).

Discussion
To the best of our knowledge, this study is the first to
provide an analysis of the effects of preoperative symp-
tom duration on each of the 3 cardinal iNPH symptoms.
Its findings can help determine which outcomes could be
expected when counseling patients with iNPH for surgery
depending on their specific preoperative symptom dura-
tion. Adding to the discourse on this topic initiated by
our group and corroborated by others, this study sup-
ports the importance of prompt diagnosis and treatment of
iNPH. Interestingly, the results suggest that patients with
iNPH with longer duration of preoperative symptoms may
not receive the same short-term benefits of surgical inter-
vention as patients with shorter duration of preoperative
symptoms, but with longer follow-up, the patients general-
ly reached the same end point. Therefore, when managing
patients with iNPH, it may take longer to see the benefits
of CSF shunting when patients present with a longer dura-
tion of preoperative symptoms.

Age stratification revealed that prolonging symptom
duration is significantly associated with lower MMSE
scores in patients 60–70 years of age and lack of cogni-
tive improvement in patients 70–80 years of age. This may
suggest that capturing improvements in cognition may be
more challenging in more elderly patients when cognitive
improvements may be more subtle. However, all of these
differences in outcomes were seen only at 6 months after
treatment and were not captured at the last follow-up visit
after treatment.

There may be some limitation to our conclusions based
on the selection of age > 40 years in the inclusion crite-
ria. There is heterogeneity in the literature regarding the
age range for the diagnosis of iNPH. According to the
international guidelines, an age threshold of 40 years
efficacy of delayed iNPH treatment

was used. In the 2012 Japanese iNPH guidelines, an age threshold of 60 years was used, and the guideline authors found that studies uncommonly found patients with an iNPH diagnosis prior to age 60. However, some studies on iNPH have included patients younger than 60 years of age, and one study include patients as young as 34 years. As the vast majority of patients in our study were treated for iNPH prior to the formulation of the 2012 Japanese iNPH guidelines, we elected to use the international iNPH guidelines, which identified an age criterion of 40 years or older for the diagnosis of iNPH. It is possible that this lower age range could lead to inclusion of patients with arrested congenital hydrocephalus, such as long-standing overt ventriculomegaly; however, the preoperative imaging requirement for normal third ventricular morphology and nonobstructive etiology should have decreased this risk. Ideally, it would be beneficial to stratify the patients by age 40–60 years versus age > 60 years, but there was not an adequate sample size to power this stratified analysis. Additionally, the median age of our patients at treatment was still 74 years, which is similar to that identified in the 2012 Japanese iNPH guidelines.

Although these results show improved outcomes with more prompt treatment, the differences between the groups treated earlier or later were lost over time, with both groups demonstrating improvement with longer follow-up. This has also been seen in prior studies. One reason for this trend may be that as patients with iNPH grow older,
other comorbidities may influence treatment outcomes. In our data, however, additional confounders may have also influenced this result. An important confounder is the heterogeneity in last follow-up time points. For some patients, the last follow-up visit was very close to surgery while others had a last follow-up visit much later in the course of their disease. The variation in the timing of the last follow-up visit can potentially mask trends. It is also possible that the lack of improvement in patients with delayed shunting may just represent further progression of the disease prior to treatment. Further studies assessing outcomes several years postoperatively would be beneficial in confirming whether the risks of delaying treatment are seen later in the disease course.

Another confounder of this study is that worse outcomes with delayed treatment may be functions of measuring outcomes later in the disease course, partly as a result of the insensitivity of our current diagnostic tests for iNPH. Patients who received delayed treatment may have ultimately ended up with the same outcome further along their presentation even had they received prompt treatment. Similarly, it is possible that since an accurate diagnosis of iNPH can be challenging, patients who presented with longer symptom duration may have had a less certain diagnosis. Nevertheless, in this study, standardized diagnostic assessments were used to identify patients with iNPH, and as shown in Fig. 1, patients with different symptom durations had similar baseline symptoms, so the certainty of iNPH diagnosis was presumably similar among the patients with different symptom durations. Furthermore, predicting how this confounder may have influenced the data can be difficult because iNPH does not progress the same way in all cases: without treatment, patients’ condition can worsen, stagnate, or even improve. Additionally, a patient’s condition may worsen because of comorbidities unrelated to their iNPH.

Finally, another inherent weakness of any study looking at symptom duration is that determining accurate symptom durations can be difficult. As previous studies have suggested, patients are often unaware that they have symptoms of iNPH. Future large population-wide prospective studies may be able to remedy some of this if a population is followed with regular, standardized assessments for iNPH, although often the disease is misdiagnosed.

While this study confirms the importance of prompt treatment for iNPH, future studies, particularly prospective multicenter registries and randomized trials, are needed to look at outcomes in patients with delayed treatment compared with patients who received no treatment and patients who received prompt treatment. Such a study would be able to correct for variables in iNPH disease presentation and disease course by comparing patients at the same stage of disease. Such studies could also benefit from closer analyses of quantitative measures of clinical outcomes, such as the MMSE, the modified Rankin Scale, the Barthel Index of Activities of Daily Living, the Wikkelsø scores, the Timed Up-and-Go test, and the Tinetti balance assessment. In our study, no statistically significant associations were found with these measures independently, probably because not all patients in this study had the tests performed as record-taking practices evolved, leading to decreased statistical power. Studies capturing associations with these quantitative clinical assessments would be able to provide granularity to these results.

Nevertheless, the results of this study are important in guiding practice toward more prompt identification and treatment of iNPH for more rapid symptom improvement. Although some may believe that the efficacy of surgery for iNPH may still be uncertain, the findings of this study reaffirm that CSF diversion surgery helps with iNPH treatment, since even with delayed treatment, by every outcome measure, improvements were seen 6 months after surgery. Indeed, the odds of no improvement in cognition, gait, and urinary incontinence were all less than 1 when preoperative symptom duration was less than 4 years.

Conclusions

This study reinforces the notion that patients with longstanding preoperative symptoms may not receive the same benefits of surgical intervention as patients with shorter duration of preoperative symptoms. However, with longer follow-up, the patients generally reached the same end point. Therefore, when treating patients with iNPH, it may take longer to see the benefits of CSF shunting when patients present with a longer duration of preoperative symptoms.

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References


Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper. This manuscript represents the views of the authors and is not meant to represent FDA’s views or policies.

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