Shunts in normal-pressure hydrocephalus: do we place too many or too few?

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Object. The average 65-year-old patient with moderate dementia can look forward to only 1.4 quality-adjusted life years (QALYs), that is, longevity times quality of life. Some of these patients suffer from normal-pressure hydrocephalus (NPH) and respond dramatically to shunt insertion. Currently, however, NPH cannot be diagnosed with certainty. The authors constructed a Markov decision analysis model to predict the outcome in patients with NPH treated with and without shunts.

Methods. Transition probabilities and health utilities were obtained from a review of the literature. A sensitivity analysis and Monte Carlo simulation were applied to test outcomes over a wide range of parameters. Using shunt response and complication rates from the literature, the average patient receiving a shunt would gain an additional 1.7 QALYs as a result of automatic shunt insertion. Even if 50% of patients receiving a shunt have complications, the shunt response rate would need to be less than 5% for empirical shunt insertion to do more harm than good. Authors of most studies have reported far better statistics.

Conclusions. In summary, many more patients with suspected NPH should be considered for shunt insertion.

Key Words • normal-pressure hydrocephalus • cerebrospinal fluid shunt • decision analysis

Although very few interventions can arrest the tragic decline of a patient with dementia, ventricular shunt insertion is effective in relieving dementia caused by hydrocephalus. Shunt placement for NPH was introduced with great enthusiasm after the pathological entity was first described in the mid-1960s. Unfortunately, the early surgical successes were not confirmed by subsequent prospective study data. Initial optimism waned, as did the rate of shunt insertion. It is clear that only a fraction of potentially eligible patients now receive shunts. The results of a recent survey of 400 patients in a memory clinic who had been referred for NPH evaluation revealed that only 71 were actually evaluated for shunt placement, and a mere 13 received shunts.

Proponents of shunt insertion have attributed the low success rate in the hands of most to inappropriate case selection, and thus a number of screening tests have been introduced to assist the clinician in selecting surgical candidates. Despite intensive study (a recent search of the MEDLINE database yielded more than 1500 publications on the topic since 1965), NPH has not been positively established as a unique clinicopathological entity. There is no gold standard for establishing its prevalence or even its presence in an individual case. Although suggested guidelines for treatment selection are plentiful, a recent Cochrane Database Review revealed that there has never been a randomized controlled trial to justify them. The sole practical test for NPH is the patient’s response to shunt insertion, and even that test has been called into question. Silverberg and colleagues have proposed a pathophysiological connection between Alzheimer disease and NPH, reviving an older theory that both diseases are shunt-responsive.

We lack clear indications for shunt surgery in demented seniors. Furthermore, given that this surgery is not free of risk, we cannot predict whether a shunt will produce more harm than good in these patients. Indeed, authors of one recent review have concluded that “shunt insertion carries a risk disproportionate to the potential benefit for these patients.” Little progress can be made until we have a basis against which proposed screening studies can be tested for sensitivity, specificity, and predictive value. Establishing a baseline can only be done by inserting shunts in all suspected cases of NPH, something we proposed in this very journal more than 30 years ago. However, it has become clear that such a study is not likely to be performed. In its place, we reviewed the relevant literature and constructed a decision analysis model to evaluate the effect of shunt insertion in patients with NPH, compared with the natural history of the demential illness.

Clinical Material and Methods

We performed a structured literature search of the MEDLINE database for the years between 1966 and 2004 by using the medical subject headings “hydrocephalus, normal pressure” and “hydrocephalus, adult (> 45 years old).” From the 1559 articles found, we eliminated case reports,
animal experiments, letters, reviews without original data, and articles dealing solely with diagnosis or pathophysiological factors. We also limited our review to English-language publications, and we supplemented this list with bibliographies of selected publications and the “Related Articles” feature of PubMed.

The 91 articles retrieved were used to estimate shunt response and complication rates. We used data summaries in the comprehensive review by Hebb and Cusimano, together with additional case studies, to calculate transition probabilities in our model. Hebb and Cusimano limited their analysis to studies in the CT era and to patients with shunts who had met each group of investigators’ criteria for idiopathic NPH. In addition to their pooled response and complication rates, we analyzed the following: additional studies from the pre-CT era and after the publication of Hebb and Cusimano’s report (but using their criteria); studies that included all adult patients with shunts (that is, those with idiopathic NPH, Alzheimer disease and other dementias, or secondary NPH); a best case scenario (all improvements not otherwise specified were assumed to be significant); and a worst case scenario (all patients evaluated for and excluded from shunt insertion were considered to have had unsuccessful shunt procedures). We reviewed data from the same studies to determine shunt complication rates. When possible, data were divided into complications occurring in the 1st year postinsertion and those occurring later. From the average duration of follow up and the number of patients in each study, an annual rate of complications 1 year after shunt placement was calculated.

Annual pooled mortality rates for each age were taken from the 2000 US Census figures and adjusted upward for dementia by approximately 20% per year. Health utilities were correlated with the degree of dementia, and the effects of various interventions were estimated. This evidence is summarized in Table 1. We performed a decision analysis using Monte Carlo–Markov model techniques to simulate the course of 1000 patients with suspected NPH, which enabled us to compare the outcomes over time in individuals who had received shunts with the outcomes in those left untreated. The outcomes were measured in QALYs. A multistate time-dependent transition decision model was constructed using a commercially available software package (TreeAge Pro 2005; TreeAge Software, Williamstown, MA). The model utilized transition cycles of 1 year with a half-cycle correction, and future QALYs were discounted at 3% per year.

Markov transitions for untreated cases were limited to continued deterioration and death. Transition possibilities for patients with shunts are illustrated in Fig. 1.

We took as our base case a 65-year-old patient with suspected NPH and moderate dementia, as defined by The Consortium to Establish a Registry for Alzheimer’s Disease criteria, which permitted us to calculate the health utilities of this and subsequent clinical states. For the purposes of our model, a significant response to shunt insertion would improve conditions in our base case to mild dementia. The model estimates a 10% annual decline of health utility, although successful shunt placement arrests this deterioration. The Monte Carlo simulation utilized 1000 trials of 1000 patients each; mean outcomes and 95% CIs were calculated, as were incremental differences between shunt insertion and no treatment.

Results
In our base case, shunt insertion added a mean of 1.7 QALYs. We performed a one-way sensitivity analysis of the model, testing the effect that varying each major parameter within its 95% CI would have on outcome (Fig. 2). The shunt response rate and shunt complication rate had the greatest influence on outcome. Parameters not shown had a negligible effect on outcome. A two-way sensitivity analysis (Fig. 3) revealed that for all published rates of shunt response and complications, the outcome of placing a shunt in all patients with suspected NPH is considerably better than the natural history of the disease. Indeed, shunt insertion was worse than the natural disease history only in cases in which the shunt response rate was so low and the complication rate so high that adverse shunt sequelae outweighed the modest benefits. For example, even if the shunt complication rate was 50%, the average patient would be harmed by the shunt (compared with no treatment) only if the shunt response rate was 5% or less. For a shunt complication rate of 30%, the threshold was a response rate of less than 2.5%.

In the Monte Carlo simulation, a significant benefit was observed in the shunt-treated group, with the average patient receiving an additional 1.7 QALYs in the pooled results reported by Hebb and Cusimano (Table 2). A similar significant advantage of shunt insertion was maintained when the simulation was run for each of the other published shunt response rates (Table 1), including the worst case scenario.

Discussion
Not long after giving NPH its name, Hakim and Adams provided the disorder with a plausible pathophysiological explanation. In turn, this theoretical framework was the basis for the screening tests used to distinguish NPH from cerebral atrophy, which resulted in a self-fulfilling prophecy—only patients fitting this preconception of NPH received shunts. However, it soon became evident that neither the proposed pathogenesis nor the diagnostic study da-
ta could explain why shunt results in idiopathic NPH were inferior to those in hydrocephalus caused by other diseases. There are now many reasons to question the validity of this framework and, indeed, to question the existence of NPH as a single clinical or pathological entity.

Several theories have been advanced to explain our inability to predict shunt response in idiopathic NPH. Among them are confusing clinical and radiographic similarities to Alzheimer disease and subcortical arteriosclerotic encephalopathy, complicating comorbidities, and disease duration. Others have stressed technical factors such as the opening pressure, the type or placement of the shunt valve, or the frequency of technical shunt failures. We must emphasize that the diagnosis of idiopathic NPH can be considered only after brain tumors, endocrinopathies, and other treatable causes of dementia have been excluded.

In addition, every clinical trial of cerebrospinal fluid diversion for NPH has utilized its own criteria for inclusion and for determining clinical response, thus making comparisons difficult if not impossible. Despite the aforementioned doubts about the wisdom of predicting patient response, authors of the most recent clinical trials have continued to exclude potential candidates from shunt insertion on the basis of clinical and laboratory findings. The few recent trials in which rigid criteria were not used to select patients for surgery suggest that selection is not justified. The experience in the Dutch Normal-Pressure Hydrocephalus Study, a well-run multicenter trial, is instructive in this regard. All enrolled participants fulfilled a number of clinical and radiographic criteria, and all underwent pre–shunt insertion measurement of cerebrospinal fluid outflow resistance. Of the 95 patients who completed the trial, outflow resistance was elevated (>18 mm Hg/ml/min) in 36, and 30 (83%) of these 36 patients experienced improvement after shunt insertion. The authors concluded and continue to maintain that outflow resistance is a useful predictor of shunt outcome. Nonetheless, an examination of their 1997 findings reveals that the low sensi-

![Fig. 2. One-way sensitivity analysis illustrating the influence of important parameters on the outcome of shunt insertion. The vertical dashed line represents the expected outcome of shunt placement in the base case (3.08 QALYs). Each horizontal bar represents the effect on outcome that results from varying each major variable within its 95% CI.](image)

![Fig. 3. Two-way sensitivity analysis demonstrating the results of shunt insertion in patients with suspected NPH, compared with the natural history of NPH. Plotted shunt response and complication rates show the values at which shunt insertion improves or worsens outcome. Values plotted from the literature (see Table 1) all support shunt use (lines represent the means with 95% CIs).](image)


TABLE 1
Evidence for transition and utility values*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of Patients</th>
<th>Value</th>
<th>95% CI</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>significant shunt response rate†</td>
<td>721</td>
<td>0.290†</td>
<td>0.257–0.323</td>
<td>40</td>
</tr>
<tr>
<td>base case-response rate—all idiopathic NPH§</td>
<td>1450</td>
<td>0.314‡</td>
<td>0.290–0.338</td>
<td>2, 6–8, 24, 26, 29, 34, 36, 40, 41, 46, 76, 120</td>
</tr>
<tr>
<td>significant shunt response rate—all patients w/ shunts</td>
<td></td>
<td>2367</td>
<td>0.262§</td>
<td>0.244–0.280</td>
</tr>
<tr>
<td>best case scenario*‡</td>
<td>3114</td>
<td>0.553§</td>
<td>0.536–0.570</td>
<td>75, 78, 83, 84, 86, 90, 93–95, 97, 114, 117, 118, 2235, 0.140§</td>
</tr>
<tr>
<td>worst case scenario†</td>
<td>2480</td>
<td>0.250§</td>
<td>0.233–0.267</td>
<td>99, 101, 105, 107, 112, 117, 118, 2111, 0.245§</td>
</tr>
<tr>
<td>perioperative complications</td>
<td>3114</td>
<td>0.033§</td>
<td>0.027–0.040</td>
<td>121</td>
</tr>
<tr>
<td>complication-related shunt deaths</td>
<td>2235</td>
<td>0.140§</td>
<td>0.126–0.154</td>
<td></td>
</tr>
<tr>
<td>shunt complication rate—1st yr</td>
<td>2111</td>
<td>0.245§</td>
<td>0.227–0.263</td>
<td></td>
</tr>
<tr>
<td>annual shunt complication rate—after 1st yr</td>
<td>890</td>
<td>0.019§</td>
<td>0.011–0.025</td>
<td></td>
</tr>
<tr>
<td>annual mortality rate—shunt responders NA‡‡</td>
<td>NA‡‡</td>
<td>NA‡‡</td>
<td>NA‡‡</td>
<td>4</td>
</tr>
<tr>
<td>annual mortality rate—natural history §§</td>
<td>NA</td>
<td>20% &gt; normal‡</td>
<td>NA</td>
<td>22</td>
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</table>

health utilities

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>moderate dementia</td>
<td>NA</td>
<td>0.53</td>
</tr>
<tr>
<td>mild dementia (shunt response)</td>
<td>NA</td>
<td>0.69</td>
</tr>
<tr>
<td>having shunt inserted</td>
<td>NA</td>
<td>0.9</td>
</tr>
<tr>
<td>having 1st shunt complication</td>
<td>NA</td>
<td>0.75</td>
</tr>
<tr>
<td>having 2nd shunt complication</td>
<td>NA</td>
<td>0.5</td>
</tr>
</tbody>
</table>

* NA = not applicable.
† Significant response as defined by Hebb and Cusimano, 2001.
‡ Mean value.
§ Data from Hebb and Cusimano, 2001, plus series from pre-CT era and after 2001.
** Assumes all patients who did not receive shunts would not have had significant responses.
†† Assumes all positive shunt responses are significant.
‡‡ Rate increases yearly with age. See 2000 US Census figures.
§§ Untreated, no response to shunt, or shunt removed due to multiple complications.

As with all models, we made several simplifying assumptions that may have affected our results. We assumed that the death rate for untreated NPH is the same as that for Alzheimer disease and that once a shunt is successful, the mortality rate returns to that of a healthy individual of the same age. We also assumed that patients in whom shunt placement had failed would not undergo shunt reinsertion after complications occurred. In contrast, patients whose conditions responded to a shunt would undergo a second attempt at shunt placement after a complication. Moreover, we assumed that the rate of complications with second shunts would be the same as with the first. Shunt response and complication rates vary widely; however, we attempted to encompass the reported spectrum in our estimates. We limited the utility of NPH to its effect on cognition. Although gait disturbance and incontinence are potentially important, their significance varies too much from case to case to allow quantification. The utilities we assigned the various interventions and complications are estimates not based on actual patient preferences; however, their effects on outcomes were minimal. We used a base case of a 65-year-old patient. The effectiveness of shunt placement is obviously lower in older patients (higher in younger), although the same relative outcomes apply.

The effectiveness of placing a shunt in all cases of suspected NPH was found to be 1.7 QALYs greater than in the untreated group. This number is misleading, however, given that fewer than one third of the patients in the model responded to a shunt. Among those who did respond, the gain was 6.2 QALYs, an effectiveness roughly equal to that of coronary artery bypass graft and breast cancer surgery for appropriate patients of the same age.70,120

We must seek a balance between limiting shunt placement in patients guaranteed to respond and offering treatment to the widest possible group of recipients, a group whose future is otherwise grim. Our model suggests that under all but the most extreme circumstances, the average 65-year-old patient suspected of having NPH is considerably more likely to benefit than to suffer from shunt placement. This model is limited by its many assumptions, as are all such decision analysis approaches. We would not favor shunt insertion if the balance between the benefit and the risk is very close. Nevertheless, the model’s conclusions appear robust and unequivocal. Even if our estimates are erro-

TABLE 2
Shunt insertion and outcome in suspected NPH

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Expected Outcome (QALYs)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>no treatment</td>
<td>1.391</td>
<td>1.323–1.453</td>
</tr>
<tr>
<td>shunt placement for all</td>
<td>3.082</td>
<td>2.705–3.446</td>
</tr>
<tr>
<td>incremental effectiveness*</td>
<td>1.691</td>
<td>1.337–2.047</td>
</tr>
</tbody>
</table>

*Refers to the difference in effectiveness between the first two strategies.
neous, the margin in favor of shunt insertion is so substantial that our conclusion is still valid. It remains to be seen whether tests are available to screen candidates for shunt surgery in a cost-effective manner. These questions will be explored in a companion article.

**Conclusions**

In this simulation of shunt outcome in cases of suspected NPH, the results favor shunt placement in many more patients than are presently being considered for the surgery. The expected outcome in a patient with moderate dementia is better than the natural history of NPH over a wide range of shunt response and complication rates, including those reported in most surgical studies.

**Appendix**

**Decision Analysis Model**

We constructed a decision tree, comparing all probable outcomes from the two management options (Fig. 4). The tree consists of a number of nodes joined by branches. Each branch represents the probability of transitioning from the node along that branch. The square node signifies the point at which a therapeutic decision is made. The round chance nodes represent branchings determined by chance. Nodes containing the letter M are Markov nodes. A Markov model repeats the transitions in regular intervals—in this case, annually and until all patients have died. As an example, a successful shunt surgery leaves the patient well. Each year, he or she may remain well, suffer shunt complications, or die. The complication rate is highest the 1st year after shunt insertion and remains constant thereafter. The annual death rate increases every year after the age of 65 years at a rate reported by the 2000 Census (and adjusted upward for the degree of dementia).

Uncertainty in the model can be handled in two ways. In a sensitivity analysis, one or more parameters are systematically varied along the possible values, and the effect on the expected outcome is investigated. Figure 2 is an example of a one-way sensitivity analysis in which parameters are varied individually. Figure 3 represents a two-way sensitivity analysis, involving simultaneous variation of the two most important parameters: shunt response and shunt complication rates. The figure illustrates the optimal strategies for different rates and the threshold at which the optimal strategy changes.

Another way to incorporate uncertainty is a Monte Carlo simulation in which a clinical trial is simulated. In the second-order simulation we utilized, 1000 simulated patients travel randomly through the tree, their paths based on the probability distributions at each encountered node. Each patient cycles through the Markov nodes until death, and the individual number of QALYs is calculated and averaged for the entire trial of 1000 patients. Each new trial randomly re-samples the probability distributions; statistics for the thousand trials are summarized in Table 2.

**Disclosure**

None of the authors has a financial interest in the subject under discussion.

**References**

2. Anderson RC, Grant JJ, de la Paz R, Frucht S, Goodman RR: Volumetric measurements in the detection of reduced ventricular...


17. Bradley WG: Normal pressure hydrocephalus and deep white matter ischemia: which is the chicken, and which is the egg? AJNR Am J Neuroradiol 22:1638–1640, 2001


27. Dunn L: “Normal pressure hydrocephalus”: what’s in a name? J Neurol Neurosurg Psychiatry 73:8, 2002 (Editorial)


S. C. Stein, M. G. Burnett, and S. S. Sonnad
Shunt placement for normal-pressure hydrocephalus


45. Ishikawa M: [Idiopathic normal pressure hydrocephalus-regarding the guideline in progress. ] Nippon Rinsho 62 (Suppl)290–294, 2004 (Jpn)


88. Schmitt J, Spring A: [Therapy of normal pressure hydrocephalus with the transcutaneously magnetically adjustable shunt.] Neurorochirurgia (Stuttg) 33 Suppl 1:23–26, 1990 (Ger)


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