The pathogenesis of normal-pressure hydrocephalus (NPH) is thought to consist of disturbed absorption of cerebrospinal fluid (CSF) caused by an increase in the resistance to outflow of CSF ($R_{csf}$), resulting in an increase in CSF pressure and ventricular dilation. This mechanism is not disputed for symptomatic NPH but is largely unexplained for idiopathic NPH. According to the few neuropathological studies of idiopathic NPH, leptomeningeal fibrosis was often absent or it was unclear whether this fibrosis was severe enough to impair absorption of CSF. The lack of correlation between $R_{csf}$, baseline CSF pressure, and ventricular size also indicates that increased $R_{csf}$ is not the only causative factor.

Several authors have drawn attention to the association between cerebrovascular disease and idiopathic NPH. Risk factors for cerebrovascular disease were found significantly more often among patients with NPH than among controls. Evidence of cerebrovascular disease such as white matter hypodense lesions on computerized tomography (CT) scanning was also more common among patients with NPH. Two studies provide evidence that the association of cerebrovascular disease and NPH is indicative of an unfavorable prognosis for the results of shunt placement.

In the Dutch NPH Study 101 patients with mainly idiopathic NPH underwent placement of a ventriculoperitoneal (VP) shunt and were followed for 1 year. The objectives of this study were to determine the relative frequencies of cerebrovascular disease and four of its risk factors in this group of patients with NPH and to assess the influence of both cerebrovascular disease and risk factors on the outcome of shunt placement. A secondary aim was to examine whether our data support a causal relationship between cerebrovascular disease and NPH.

**Object.** This study was conducted to determine the prevalence of cerebrovascular disease and its risk factors among patients with normal-pressure hydrocephalus (NPH) and to assess the influence of these factors on the outcome of shunt placement.

**Methods.** A cohort of 101 patients with NPH underwent shunt placement and was followed for 1 year. Gait disturbance and dementia were quantified using an NPH scale and handicap was determined using a modified Rankin scale (mRS). Primary outcome measures consisted of the differences between preoperative and last NPH scale and mRS scores. The presence of risk factors such as hypertension, diabetes mellitus, cardiac disease, peripheral vascular disease, male gender, and advancing age was recorded. Cerebrovascular disease was defined as a history of stroke or a computerized tomography (CT) scan revealing infarcts or moderate-to-severe white matter hypodense lesions.

The prevalence of risk factors for cerebrovascular disease was higher in the 45 patients with cerebrovascular disease than the 56 without it. Risk factors did not influence outcome after shunt placement. Intent-to-treat analysis revealed that the mean improvement in the various scales was significantly less for patients with a history of stroke (14 patients), CT scans revealing infarctions (13), or white matter hypodense lesions (32 patients) than for those without cerebrovascular disease. The proportion of patients who responded to shunt placement was also significantly lower among patients with than those without cerebrovascular disease ($p = 0.02$).

**Conclusions.** The authors identified a subgroup of patients with NPH and cerebrovascular disease who showed disappointing results after shunt placement. Cerebrovascular disease was an important predictor of poor outcome.

**Key Words** • normal-pressure hydrocephalus • ventriculoperitoneal shunt • outcome • vascular risk factors • white matter hypodense lesion • cerebrovascular disease
TABLE 1

<table>
<thead>
<tr>
<th>Improvement</th>
<th>NPH Scale (%)</th>
<th>mRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>&lt;15</td>
<td>&lt;1</td>
</tr>
<tr>
<td>moderate</td>
<td>15–29</td>
<td>1</td>
</tr>
<tr>
<td>marked</td>
<td>30–44</td>
<td>2</td>
</tr>
<tr>
<td>excellent</td>
<td>≥45</td>
<td>≥3</td>
</tr>
</tbody>
</table>

* NPH scale = gait scale + dementia scale.

Clinical Material and Methods

Measurement of Gait Disturbance and Dementia

Gait disturbance was quantified using a gait scale that evaluates the presence of 10 gait features and measures the number of steps and seconds required for a 10-m walk. Dementia was assessed using a dementia scale composed of the 10-word test, digit span forward and backward, trail making, and finger tapping. To create one neurological outcome measure, the scores for gait (range 2–40) and dementia (range 4–40) were added, yielding the NPH scale (range 6–80). The modified Rankin scale (mRS), which was used to obtain a handicap score, was extended to a 7-point scale by inserting Grade 4 (defined as moderate disability; partially independent, needing assistance for less than 50% of the day).

Eligibility Criteria

Between September 1990 and July 1995 101 patients with NPH (89 idiopathic and 12 chronically symptomatic) were enrolled after fulfilling the inclusion criteria: 1) a gradually developing gait disturbance of both legs that was unexplained by other conditions and a gait scale score of at least 12; 2) a mild-to-moderate cognitive deficit without aphasia emerging together with or after the gait disturbance and a dementia scale score of at least 12; 3) a handicap mRS score of at least 2; and 4) a CT scan demonstrating a communicating hydrocephalus with an Evans’ index of 0.3 or more and a ventricular index greater than 0.8, without clinically relevant parenchymal lesions, the sum of the four largest convexity sulci being less than 25 mm (real size).

Exclusion criteria consisted of acute or subacute symptomatic NPH within 3 months of a causative incident, age 85 years or older, severe comorbidity with restricted life expectancy, or contraindications for surgery.

Study Design

All patients underwent a lumbar constant-flow infusion test and placement of a Medos Hakim spring valve shunt, regardless of the Rcsf value. Patients were randomized for a low or medium-high working pressure. The gait and dementia scales and the mRS scores were determined prior to and 1, 3, 6, 9, and 12 months postsurgery. The CT scans were obtained preoperatively and at 1, 6, and 12 months postoperatively.

Evaluation of Cerebrovascular Disease and its Risk Factors

Six risk factors for cerebrovascular disease were recorded using the following definitions: 1) arterial hypertension; 2) diabetes mellitus; 3) cardiac disease; 4) peripheral vascular disease; and 5) male gender. Each of these factors was added to the NPH scale, and the modified Rankin scale (mRS). The scores for gait and dementia were added, yielding the NPH scale (range 6–80). The modified Rankin scale (mRS), which was used to obtain a handicap score, was extended to a 7-point scale by inserting Grade 4 (defined as moderate disability; partially independent, needing assistance for less than 50% of the day).

Outcome Measures

Primary outcome measures were the differences between the preoperative and the last NPH scale and mRS scores. The results of shunt placement were analyzed using a Student’s t-test to compare the means of the primary and secondary outcome measures found for patients with and without cerebrovascular disease. The proportions of patients exhibiting improvement in each group were compared using the chi-square test. Intent-to-treat analysis was performed using all the outcome information available at 12 months or the last follow-up review. Multiple regression analysis was performed to assess in multivariate fashion the simultaneous influence of the three com-
components of cerebrovascular disease on the outcome measures.

Results

Prevalence of Cerebrovascular Disease and Its Risk Factors

Fifty-three patients presented with at least one cerebrovascular disease risk factor, excluding age and gender (Table 2). Cardiac diseases were present in 21 patients, all of whom had ischemic heart disease; three had atrial fibrillation, and one had a history of congestive heart failure. Hypertension, cardiac disease, and peripheral vascular disease occurred more frequently in patients with cerebrovascular disease, but diabetes mellitus was evenly distributed between patients with and without cerebrovascular disease. The highest percentages of hypertension and cardiac diseases were found in patients with a history of stroke or in whom infarcts were seen on CT scanning. Patients with cerebrovascular disease were older and more often female.

In total, 45 of the 101 patients presented with one or more signs of cerebrovascular disease (Table 3). Because conditions that affect gait were considered exclusion criteria, patients who had suffered ischemic events before entry into the study did not show a residual deficit. The infarctions seen on CT scans, mostly of the lacunar type, were clinically silent because symptomatic parenchymal lesions were exclusion criteria as well.

The presence of risk factors for cerebrovascular disease did not show a correlation with the initial clinical picture. Patients with cerebrovascular disease tended to have smaller ventricles and a somewhat more severe NPH syndrome at entry into the study, as quantified by the NPH scale and mRs scores (Table 4). The Rsf in this group was significantly lower.

Using the total ischemic score, the white matter hypodense lesions on the last CT scan increased in 9%, decreased in 9%, and were unchanged in 82% of the cases. Fifteen patients suffered an ischemic stroke during the follow-up period.

Cerebrovascular Disease Related to Outcome After Shunt Placement

None of the risk factors was significantly correlated with poor outcome. The number of risk factors also did not show predictive value regarding the results of shunt placement.

According to intent-to-treat analysis, patients with a history of stroke and those with white matter hypodense lesions or infarctions on CT scans showed significantly less improvement (Table 5). The largest differences in outcome were found between the 43 patients classified as having cerebrovascular disease by at least one measure and the 53 without cerebrovascular disease. Multiple regression analysis revealed that, of the three components of cerebrovascular disease, white matter hypodense lesions and infarctions on CT scanning were significantly and independently related to adverse outcome after shunting. The R square values were 0.14 for the NPH scale and 0.11 for the mRs, meaning that 14% and 11% of the mean improvement can be explained by the two expressions of cerebrovascular disease. A history of stroke did not contribute further.

Another way to analyze outcome is to calculate the proportion of patients who responded to shunt placement, defined here as those with any improvement in the NPH scale scores (Table 1). Of the 43 patients with cerebrovascular disease, 21 (49%) were categorized as improved and 22 (51%) as unimproved, whereas 39 (74%) of the 53 patients without cerebrovascular disease responded to shunt placement and 14 (26%) did not. The difference between the two groups was significant (p = 0.02) and could not be attributed to the type of shunt used. The low- and medium-high-pressure shunts were equally distributed among the groups of patients with and without cerebrovascular disease and the results of shunt placement for the two-valve types within both groups were not significantly different.

TABLE 2

Prevalence of risk factors for CVD in 101 patients with NPH*

<table>
<thead>
<tr>
<th>Factor</th>
<th>All Patients</th>
<th>W/CVD (45 patients)</th>
<th>W/O CVD (56 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>28 (28)</td>
<td>16 (36)</td>
<td>12 (21)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>15 (15)</td>
<td>6 (13)</td>
<td>9 (16)</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>21 (21)</td>
<td>11 (24)</td>
<td>10 (18)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>4 (4)</td>
<td>3 (7)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Male gender</td>
<td>60 (59)</td>
<td>24 (55)</td>
<td>36 (64)</td>
</tr>
<tr>
<td>Age ≥74</td>
<td>52 (51)</td>
<td>27 (60)</td>
<td>25 (45)</td>
</tr>
</tbody>
</table>

* CVD = cerebrovascular disease.

TABLE 3

Prevalence of CVD in 101 patients with NPH*

<table>
<thead>
<tr>
<th>CVD</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>45</td>
</tr>
<tr>
<td>History of stroke</td>
<td>14</td>
</tr>
<tr>
<td>White matter hypodense lesions</td>
<td>69</td>
</tr>
<tr>
<td>Absent or slight (TIS 0–1)</td>
<td>32</td>
</tr>
<tr>
<td>Moderate or severe (TIS 2–4)</td>
<td>13</td>
</tr>
<tr>
<td>Infarctions on CT</td>
<td>56</td>
</tr>
</tbody>
</table>

* TIS = total ischemic score.

TABLE 4

Baseline variables related to CVD in 101 patients with NPH*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients W/ CVD (45 patients)</th>
<th>Patients W/O CVD (56 patients)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular width</td>
<td>1.16 ± 0.15</td>
<td>1.21 ± 0.16</td>
<td>0.14</td>
</tr>
<tr>
<td>Rsf</td>
<td>15.9 ± 4.3</td>
<td>18.9 ± 7.1</td>
<td>0.02</td>
</tr>
<tr>
<td>mRs</td>
<td>3.9 ± 1.0</td>
<td>3.5 ± 1.4</td>
<td>0.20</td>
</tr>
<tr>
<td>NPH scale†</td>
<td>51.4 ± 13.1</td>
<td>46.0 ± 17.1</td>
<td>0.08</td>
</tr>
</tbody>
</table>

* Values are presented as the mean ± standard deviation.
† NPH scale = gait scale + dementia scale.
of the 74 patients of Larsson, et al., 27 and 28% in the patients reported by Graff-Radford and Godersky,16 and 83% Arterial hypertension was present in 74% of the 19 patients suffering from idiopathic NPH have been studied before. 224 J. Neurosurg. / Volume 90 / February, 1999 of patients with NPH. in turn can be considered as risks in the surgical treatment dealing with risk factors for cerebrovascular disease that finding that they were not related to outcome after shunting. Such a relationship is not obvious because we are dealing with risk factors for cerebrovascular disease that in turn can be considered as risks in the surgical treatment of patients with NPH. The causes of white matter hypodense lesions are not fully understood, partly because the neurologically and histological abnormalities involved are nonspecific.31 White matter hypodense lesions are closely associated with stroke and arterial hypertension.2,8,9,19,25 Furthermore, the risk for stroke is increased in patients with white matter hypodense lesions.18,32,43 To a lesser extent white matter hypodense lesions are associated with Alzheimer’s disease,15,19 but we took particular care to exclude that condition. Patients suffering from an acute or subacute disturbance of CSF circulation may develop periventricular luencies due to transependymal CSF leakage. In this study the NPH was chronic in nature; moreover, the white matter hypodense lesions lacked the typical periventricular caps and did not change after shunt placement in the majority of cases. Therefore, we consider white matter hypodense lesions to be an expression of white matter ischemia. Although magnetic resonance (MR) imaging is more sensitive for detection of white matter hypodense lesions, CT scanning is more specific for prediction of symptomatic cerebrovascular disease.29 The occurrence of white matter hypodense lesions on MR imaging has been addressed in two studies. These lesions were detected in a significantly higher proportion of patients with NPH than controls.7,26 The prevalence of white matter hypodense lesions in patients with NPH (93%7 and 70%26) was of course higher than in our CT-based study (56%).

**TABLE 5**

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. of Patients</th>
<th>NPH Scale (%)</th>
<th>Gait Scale (%)</th>
<th>Dementia Scale (%)</th>
<th>mRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>history of stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>13</td>
<td>2.2 ± 35.5</td>
<td>6.0 ± 47.7</td>
<td>−0.3 ± 37.8</td>
<td>0.15 ± 1.77</td>
</tr>
<tr>
<td>no</td>
<td>83</td>
<td>23.7 ± 2.1</td>
<td>30.3 ± 47.2</td>
<td>14.6 ± 26.0</td>
<td>1.11 ± 1.44</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td>0.03</td>
<td>0.09</td>
<td>0.08</td>
<td>0.03</td>
</tr>
<tr>
<td>white matter hypodense lesions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>moderate or severe</td>
<td>30</td>
<td>10.2 ± 31.2</td>
<td>12.6 ± 45.1</td>
<td>4.7 ± 28.4</td>
<td>0.40 ± 1.30</td>
</tr>
<tr>
<td>absent or slight</td>
<td>66</td>
<td>25.6 ± 33.3</td>
<td>33.6 ± 47.8</td>
<td>16.1 ± 28.2</td>
<td>1.24 ± 1.54</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td>0.04</td>
<td>0.05</td>
<td>0.06</td>
<td>0.01</td>
</tr>
<tr>
<td>infarct on CT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>12</td>
<td>−5.3 ± 47.4</td>
<td>−14.7 ± 73.6</td>
<td>4.0 ± 28.0</td>
<td>0.25 ± 2.22</td>
</tr>
<tr>
<td>no</td>
<td>84</td>
<td>24.5 ± 29.3</td>
<td>33.0 ± 40.1</td>
<td>13.8 ± 28.0</td>
<td>1.08 ± 1.37</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td>0.003</td>
<td>0.001</td>
<td>0.26</td>
<td>0.07</td>
</tr>
<tr>
<td>cerebrovascular disease†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>43</td>
<td>8.3 ± 36.2</td>
<td>8.7 ± 54.7</td>
<td>5.0 ± 31.0</td>
<td>0.51 ± 1.50</td>
</tr>
<tr>
<td>no</td>
<td>53</td>
<td>30.8 ± 27.1</td>
<td>41.9 ± 35.3</td>
<td>18.7 ± 24.1</td>
<td>1.35 ± 1.42</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td>0.001</td>
<td>0.001</td>
<td>0.02</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

* Values are expressed as the mean ± standard deviation.
† Improvement was measured according to the intent-to-treat analysis.
‡ NPH scale = gait scale + dementia scale.
§ Cerebrovascular disease consisted of at least one of the following: history of stroke, moderate or severe white matter hypodense lesions, or infarctions on CT scanning.

**Discussion**

Prevalence of Cerebrovascular Disease and its Risk Factors

Risk factors for cerebrovascular disease among patients suffering from idiopathic NPH have been studied before. Arterial hypertension was present in 74% of the 19 patients reported by Graff-Radford and Godersky,16 and 83% of the 65 patients of Krauss, et al.,24 compared with 31% of the 74 patients of Larsson, et al.,22 and 28% in the present study. These considerable differences cannot be attributed to the prevalence of hypertension in control volunteers of the same age, which was approximately 35% in large stroke studies.12,41 The relative numbers of patients with NPH, percentages exceeding those reported in studies conducted in Germany and Italy10,24 and 30% in one conducted in The Netherlands.39 Part of the discrepancy can be explained by differences in definition. After excluding blood pressure measurements taken during the study, as we did, Krauss, et al.,24 still found hypertension in 60% of their patients. They also found diabetes mellitus in 49% and ischemic heart disease in 57% of the patients with NPH, percentages exceeding those reported in large stroke studies.12,41 The relative numbers of patients with a history of stroke24 and lacunar infarct on CT scans16 were also higher than in our study. The populations of patients with NPH investigated by Graff-Radford and Godersky and Krauss, et al., were obviously different from those studied by Larsson, et al., and the present study.

Although our study of risk factors for cerebrovascular disease was not complete (the smoking history and cholesterol levels in our patients are missing), it is unlikely that inclusion of these two factors would have altered the finding that they were not related to outcome after shunting. Such a relationship is not obvious because we are dealing with risk factors for cerebrovascular disease that in turn can be considered as risks in the surgical treatment of patients with NPH.

The causes of white matter hypodense lesions are not

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sults of CSF shunting. Because four of seven patients with the most severe white matter hypodense lesions responded to shunt placement, we agree with Krauss, et al.24 that these patients should not automatically be denied this treatment. In contrast to their findings, we could not demonstrate a relationship between white matter hypodense lesions, preoperative NPH, and mRS scores.

Both a history of stroke and the presence of infarctions on CT scans were predictors of an unfavorable outcome. The greatest difference in mean improvement was found between patients with at least one expression of cerebrovascular disease and those without. In a study of 74 carefully evaluated patients with NPH the least improvement was also obtained in a subgroup with NPH secondary to cerebrovascular disease.33 The high percentage of our patients suffering from stroke during the 1-year follow-up period further underlines the importance of cerebrovascular disease in idiopathic NPH and could be a reason to refrain from shunt placement in doubtful cases.

Pathogenetic Role of Cerebrovascular Disease

The question is whether cerebrovascular disease may actually cause NPH. The neuropathological evidence is meager. Examination of 25 brain biopsy specimens obtained in patients with suspected NPH revealed meningeal fibrosis in only 12 and signs of Alzheimer’s and cerebrovascular disease in 10 cases, suggesting that NPH may be a parenchymal disease in a number of patients.1 Autopsy findings showed hypertensive cerebrovascular disease with normal leptomeninges and arachnoid villi in some patients who presented with the typical clinical and radiological features of NPH.1,13,17 The postmortem findings in seven patients with NPH consisted of bothBinswanger’s encephalopathy and focal leptomeningeal fibrosis, as well as reduction of arachnoidal granulations.1

An answer to the previously mentioned question is thwarted by the difficult clinical diagnosis of NPH, in particular its distinction from Binswanger’s disease. According to Gallassi, et al.,14 both diseases constitute a continuous spectrum that will narrow in the course of time. Patients with longstanding NPH will develop periventricular ischemia, and ventricular size will increase in Binswanger’s disease.

A review of the literature on CSF dynamics in NPH indicates that most investigators agree that increased Rsfc is the primary pathogenetic factor. However, a few hold the view that changes in compliance are the initial cause of ventricular dilation.36,37 Hydrocephalus could be induced in animals by increasing the intraventricular pulse pressure; increasing pulse pressures were recorded before an increase in intracranial pressure was seen in patients who developed hydrocephalus after subarachnoid hemorrhage.35 These observations provide some support for the notion that arterial hypertension might cause NPH by increasing the intraventricular pulse pressure, especially because an increased pulse pressure is more common in cases of hypertension in elderly patients.34 White matter hypodense lesions and deep white matter infarctions supposedly are more important for the development of NPH.2,13 The vascular lesions will result in a reduction in the volume of periventricular tissue. This process is enhanced by a decrease in periventricular compliance, causing larger intraventricular CSF pulsations that push the ventricular wall outward. As the surface of the ventricular wall increases, the water hammer force on that wall increases as well. Subsequently, the arachnoidal space at the convexity may be compressed, producing an increase in Rsfc.

What evidence from our study supports a causative role of cerebrovascular disease in idiopathic NPH? We could not find a relationship between Rsfc, ventricular size, reduction of ventricular size after shunt placement, severity of the NPH syndrome at entry to the study, and degree of improvement after shunt placement, indicating that NPH is not an entity but a syndrome with varied underlying causes. Also, patients with NPH and cerebrovascular disease demonstrated a lower Rsfc, possibly indicating parenchymal involvement rather than a CSF circulation disorder. Furthermore, patients with moderate or severe white matter hypodense lesions exhibited slightly irregular ventricular walls explainable by retraction of periventricular tissue. On the other hand, one might argue that cerebrovascular disease occurs incidentally in a subgroup of patients with NPH. Some of the white matter hypodense lesions and infarctions were located in the deep white matter and not periventricularly, as presumed by the compliance hypothesis. The findings in a previous study were not in agreement with this hypothesis either.39 We demonstrated in a large group of hydrocephalic patients that compliance was not an independent parameter but was chiefly determined by Rsfc. Finally, the periventricular parenchymal changes that reduce compliance seem largely irreversible, which is less compatible with findings of improvement after VP shunt placement.

Conclusions

The prevalence of cerebrovascular disease in patients with NPH is high. Cerebrovascular disease is an important predictor of an unfavorable outcome of VP shunt placement, although not to such a degree that this operation should be discouraged beforehand. The difficult question of a causal relationship between cerebrovascular disease and NPH is not settled. A study that includes a larger number of patients with NPH and that is specifically designed to evaluate cerebrovascular disease is required.

References


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Address reprint requests to: Joseph T. J. Tans, Ph.D., Westeinde Hospital, P.O. Box 432, 2516 CK The Hague, The Netherlands.