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d u t c h
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p r e s s u r e
hydrocephalus
s t u d y

THE DUTCH NORMAL- PRESSURE HYDROCEPHALUS STUDY

(het Nederlandse onderzoek naar normale druk hydrocephalus)

PROEFSCHRIFT

**TER VERKRIJGING VAN DE GRAAD VAN DOCTOR AAN DE
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OP GEZAG VAN DE RECTOR MAGNIFICUS**

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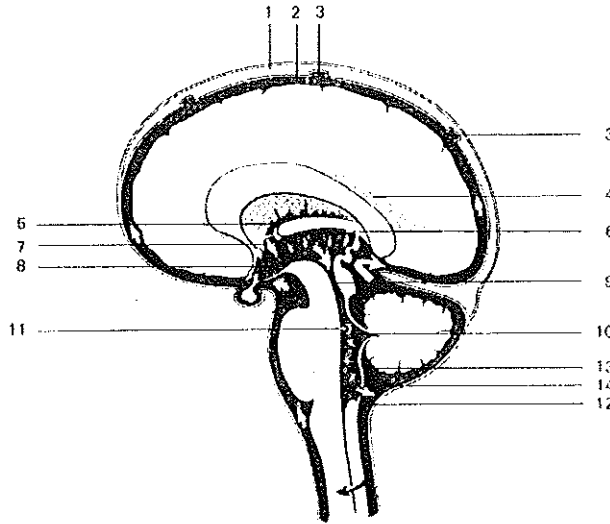
GENERAL INTRODUCTION

In 1965 Hakim and Adams described 6 patients with a mild impairment of the memory, slowness and paucity of thought and action, unsteadiness of gait and unwitting urinary incontinence.^{1;46} These symptoms had evolved over a period of weeks or a few months. The pneumoencephalogram of these patients showed a quadriventricular hydrocephalus with no air in the cerebral subarachnoid spaces. A normal cerebrospinal fluid (CSF) pressure was measured by lumbar puncture. They all dramatically improved on CSF shunting. Hakim and Adams named this syndrome of symptomatic occult hydrocephalus with normal CSF pressure normal-pressure hydrocephalus (NPH). Afterwards many patients were described with the clinical triad of a gait disturbance, mental deterioration and urinary incontinence in combination with a communicating hydrocephalus on computed tomography and a normal CSF pressure. In studies on dementia NPH was found in 0% to 5.4% of the study population.^{9;54;55;67;79;123}

NPH should be distinguished from acute hydrocephalus, in which CSF pressure is increased and headache, nausea, vomiting, and visual symptoms are present, and from chronic high-pressure hydrocephalus in which symptoms and signs of increased pressure are less pronounced. Symptomatic cases of NPH mainly follow subarachnoid hemorrhage, trauma, meningitis or intracranial surgery. Many cases, especially over the age of 60, have no known cause and are therefore idiopathic.

Although the full pathophysiology is unknown, a deficit in CSF absorptive capacity seems to be a primary pathogenic factor.^{1;18;25;46;74;133} The blockage of CSF outflow pathways by blood or infection in the CSF spaces (Fig.1.1) is easily understood, but the explanation is less clear in idiopathic NPH. Ventricular dilatation requires the presence of a pressure gradient between the subarachnoid space at the convexity and the ventricles at one point in time. Subsequently, the intraventricular pressure will decrease to normal values, but the ventricles remain enlarged and can even enlarge further probably due to altered structural properties of the periventricular tissue and hydrodynamic mechanisms, such as persistence of a transmante pressure gradient.¹²⁸ The development of the symptoms can be attributed to dysfunction of periventricular structures.

Fig. 1.1. CSF pathways



CSF is produced by the choroid plexus of the lateral ventricles (5), of the third (6) and fourth (13) ventricle. From the lateral ventricles (4) CSF gains exit through the foramina of Monro (7) into the third ventricle (8) and from here through the aqueduct of Sylvius (9) into the fourth ventricle (10). The outer CSF spaces, such as the cisterna magna (14), are reached through the foramina of Luschka (11) and Magendie (12). CSF then circulates through the subarachnoid spaces of the spinal cord and the brain to the convexity (2). There CSF enters the superior sagittal sinus (1) by absorption via the arachnoid villi (3). Adapted from Oosterhuis⁸⁶

The signs and symptoms of NPH may show a dramatically good response to CSF diversion by a ventriculoperitoneal or ventriculoatrial shunt. However, results of shunting reported by various investigators differ considerably, largely due to methodological differences. Major factors affecting outcome after shunting are the length of follow-up, the inclusion or exclusion of comorbidity, the proportion of idiopathic and symptomatic cases and the definition of outcome criteria. In studies with at least 50 cases 36 to 83% of the patients improved (Table 1.1).^{11;18;26;42;53;70;80;80;97;99;106;122;129;136}

An important reason for the somewhat disappointing results of shunting is that the clinical diagnosis of NPH is difficult. Gait, cognitive and micturition disturbances occur in many neurological and non-neurological conditions of the elderly. Furthermore, shunting procedures have a high complication rate. Subdural effusions occur in up to 28%,^{10;11;18;42;49;69;70;81;90;100;122} shunt dysfunction in 6 to 31%^{10;18;42;49;69;80;129} and shunt infections in up to 19% of the cases (Table 1.1).^{13;42;69;70;80;90;106;107;122} These frequent complications cause an understandable reluctance with respect to shunt placement.

complications cause an understandable reluctance with respect to shunt placement. Finally, a diagnostic test that enables reliable identification of those patients with NPH who will respond to shunt placement, was not available.

Table 1.1. Outcome of shunt placement and shunt-related complications in patients with NPH, as reported in previous studies.

Author	Year	Patients Included / Evaluable (N)	Outcome (N)	Subdural Effusions (N)	Shunt Infections (N)	Shunt Dysfunction (N)
Benzel ¹⁰	1990	37	26	6		
Black ¹¹	1980	62	29	6		
Börgesen ¹⁸	1984	64 / 56	37	4	4	4
Delwel ²⁸	1989	50	30			
Greenberg ⁴²	1977	73 / 68	33	2	4	9
Hughes ⁴⁹	1978	27	9	6		3
Janny ⁵³	1981	56 / 47	22	4	0	2
Larsson ⁶⁹	1991	74 / 71	58	7	14	23
Laws ⁷⁰	1976	56	28	8	1	11
McQuarrie ⁸⁰	1984	72	29	3	1	
Petersen ⁹⁰	1985	45		7	2	9
Sahuquillo ⁹⁷	1991	65	54			
Salmon ⁹⁹	1972	80 / 74	34	0	10	
Samuelson ¹⁰⁰	1972	24		5		
Spanu ¹⁰⁸	1986	54 / 50	39		2	
Stein ¹⁰⁷	1974	43	29		1	4
Udvarhelyi ¹²²	1974	55	33	2	10	7
Wood ¹³⁸	1974	55	33	2	10	7
Vanneste ¹²⁹	1992	166 / 152	55	23	6	

One of the diagnostic tests that is used by many investigators to select patients with NPH for shunting is measurement of the resistance to outflow of cerebrospinal fluid (Rcsf), a quantitative evaluation of the capacity for CSF absorption.⁵⁶ Katzman and Hussey were the first who described a lumbar constant flow infusion technique in 1970.⁵⁶ This method was based on the principles that under physiological steady state conditions CSF production remains constant at ± 0.35 ml/minute within a CSF pressure range of 0 - 30 cm H₂O^{24,56,95} and is balanced by the CSF absorption rate. This implies that the total

volume of CSF stored in the system does not change and the intracranial pressure (P) is maintained at a constant baseline or resting level (P_o), yielding the equation:

$$\text{CSF formation (Fi) - CSF absorption (Fo)} = 0^{5,78} \quad (1)$$

The CSF absorption rate is generally accepted to be linearly related to the pressure difference between the subarachnoidal space and the dural sinuses, as long as the intracranial pressure exceeds the dural sinus pressure (P_d). If pressure continues to rise, CSF absorption increases proportionally until a maximum is reached of 1.5 - 2 ml/minute, about five times the CSF production.^{24,56,95} CSF absorption is also determined by the outflow resistance (Rcsf):

$$F_o = (P - P_d) / R_{csf} \quad (2)$$

Subsequently:

$$F_i - (P - P_d) / R_{csf} = 0 \quad (3)$$

The baseline intracranial pressure, $P = P_o$, is then solely determined by the CSF formation rate, Rcsf and sinus pressure:

$$P_o = R_{csf} F_i + P_d \quad (4)$$

When the formation rate increases, which can be simulated by infusing artificial CSF at a constant rate into the CSF space, an infusion test, equation (1) can be rewritten as:

$$F_i + F_{inf} - F_o = 0 \quad (5)$$

The new steady state pressure (P_{pl}) can be derived from this equation:

$$P_{pl} = R_{csf} F_i + R_{csf} F_{inf} + P_d \quad (6)$$

and using equation (4):

$$P_{pl} = R_{csf} F_{inf} + P_b \quad (7)$$

Rcsf can then be computed:

$$R_{csf} = (P_{pl} - P_o) / F_{inf}^5$$

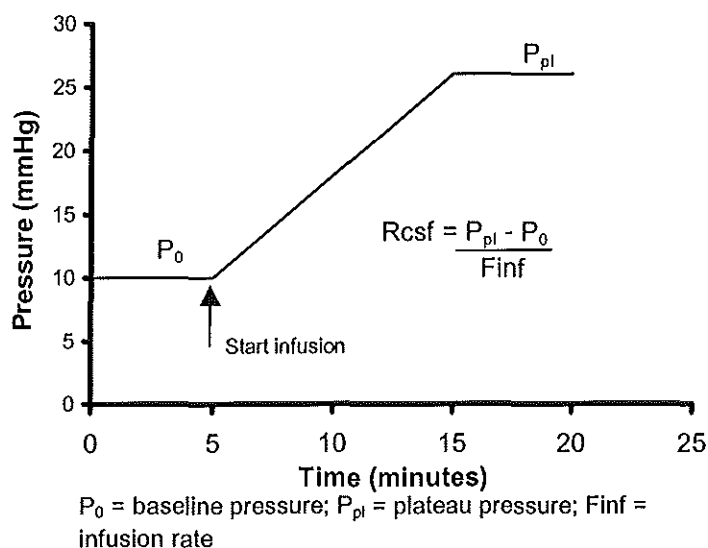
Thus, CSF outflow resistance can be calculated by dividing the difference between the new equilibrium pressure and baseline pressure by the infusion rate.

The technique of lumbar constant flow infusion requires only one lumbar puncture. The needle is connected via a three-way tube system to a pressure transducer, chart recorder and an infusion pump. After recording the baseline pressure (Fig. 1.2), saline is infused at a constant rate of 1.4 to 1.6 ml/minute into the CSF space. This rate was used to create a maximal stimulation of the absorptive capacity. The increasing volume of the CSF produces an increasing CSF pressure that causes an increase in CSF absorption. After 10 to 15 minutes of infusion the volume of infused saline plus the volume of produced CSF become equal to the volume that is absorbed, leading to a new equilibrium of pressure. Examples of infusion tests of three of our patients were shown in Fig. 1.3.

The idea of Rcsf measurement was that with an increased Rcsf the patient should improve after shunt placement. Unfortunately, conflicting results of the predictive

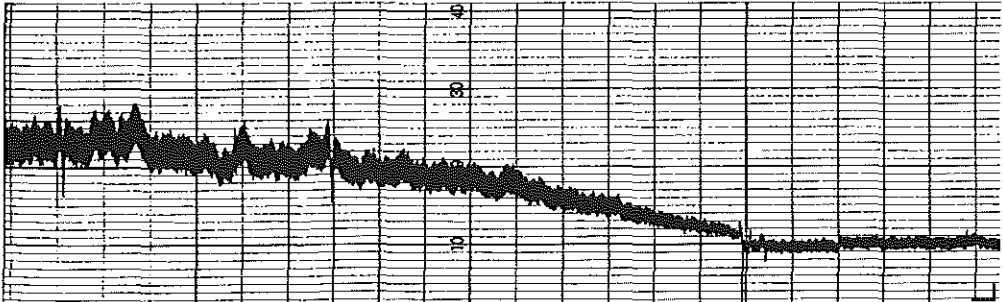
value of Rcsf regarding outcome after shunting were reported with both low^{26;41;53;60;77;107;135} and high^{19;48;66;75;84;92;113-115} predictive values. Many of these previous reports, however, suffered from limitations. The studies were carried out in single institutions by skillful, experienced investigators, interested in the field of cerebrospinal fluid dynamics. Broad applicability of Rcsf measurement has not yet been demonstrated. The diagnostic value of infusion tests was not properly evaluated, because patients with NPH received a shunt only when Rcsf exceeded a certain threshold. Therefore the negative predictive value of Rcsf is largely unknown. Finally, in most studies the number of patients was rather small and outcome measures were not clearly quantified.

Fig. 1.2. Schematic pressure curve before and during infusion

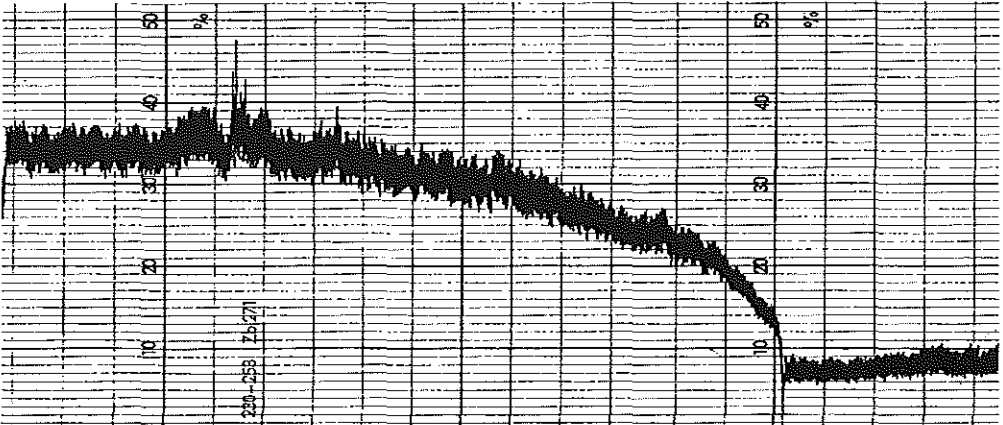


Therefore we decided to perform the Dutch Normal Pressure Hydrocephalus Study, a prospective randomized study of patients with NPH, in which 4 neurological and neurosurgical centers collaborated. The protocol of this study and the baseline characteristics, with emphasis on the clinical findings of the 101 NPH patients, are described in **Chapter 2**. The main objective was determination of the positive and negative predictive values of Rcsf, obtained with lumbar constant flow infusion, for the outcome of shunt placement. The results are presented in **Chapter 3**.

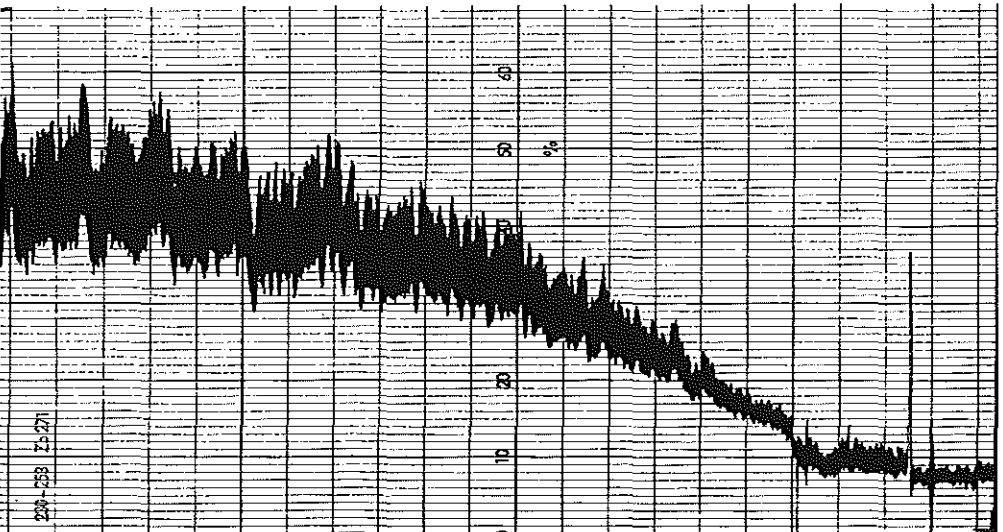
Fig. 1.3. Examples of lumbar spinal infusion tests of three of our patients



a. Po = 10 mmHg, Ppl = 23 mmHg, Rcsf = 8.1 mmHg/ml/minute



b. Po = 8 mmHg, Ppl = 34 mmHg, Rcsf = 16.3 mmHg/ml/minute



c. Po = 10 mmHg, Ppl = 45 mmHg, Rcsf = 21.9 mmHg/ml/minute

Most neurosurgeons prefer ventriculoperitoneal shunts for the surgical treatment of NPH, but there is much controversy regarding the opening or working pressure of the shunt. Commercially available shunts usually have differential pressure valves with a low, medium or high working pressure. The working pressure is the difference in pressure between inlet and outlet of the shunt at which drainage starts. Surprisingly few studies have addressed this working pressure dilemma and randomized studies comparing different working pressures have not been performed. In one retrospective study better results were observed with low pressure shunts than with medium pressure shunts.⁸⁰ The second objective of the Dutch Normal Pressure Hydrocephalus Study therefore was to determine whether low or medium pressure shunts are more effective in reversing the signs and symptoms of NPH. The results of this randomized study are reported in **Chapter 4**.

Although a disturbance of CSF absorption is thought to be the cause of the NPH syndrome, the full mechanism is still unclear, especially in idiopathic NPH. Case reports began to appear already in the seventies pointing to a possible association between cerebrovascular disease (CVD) and idiopathic NPH. Some patients with the clinical picture of NPH were found to have a severe hypertensive encephalopathy at autopsy or white matter hypodense lesions with or without small deep infarcts on computed tomography.^{2;28;45;61;74;85;93} Attention was drawn to clinical and computed tomographic similarities between Binswanger's disease and NPH.^{36;94} Risk factors for CVD, such as hypertension, diabetes mellitus and cardiac disease, were found more often in NPH patients than in controls.^{23;40;63} It was hypothesized that periventricular vascular disease could be the cause of the NPH syndrome in a subgroup of patients.^{20;28;45;61} The prognosis for this subgroup seemed to be less favorable.^{62;69;103} The results of our investigation of the prevalence of CVD and risk factors for CVD in the 101 NPH patients, in particular the influence of CVD on outcome after shunt placement can be found in **Chapter 5**. Whether our data support a possible causal relationship between CVD and NPH will be discussed as well.

In view of the disappointing results of diagnostic tests, the importance of the presence of the clinical triad for the prediction of outcome has been stressed repeatedly.^{10;13;90} The value of combined CT and clinical findings in predicting outcome was reported as well.¹³⁰ So, the question that has to be answered is what is the additional value of Rcsf? Therefore, we compared the prognostic values of clinical and computed tomographic findings, separately and in relation to Rcsf measurement and the presence CVD in **Chapter 6**. This analysis also offered the opportunity to integrate the different parts of the Dutch Normal Pressure Hydrocephalus Study and to present an algorithm for the selection of patients for shunt placement.

2

BASELINE CHARACTERISTICS WITH EMPHASIS ON CLINICAL FINDINGS

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ABSTRACT

We present the baseline characteristics of 101 patients with normal pressure hydrocephalus (NPH), entering a study that evaluates the diagnostic reliability of CSF outflow resistance. Patients were assessed by a gait scale, consisting of 10 features of walking and the number of steps and seconds necessary for 10 m, a dementia scale, comprising the 10 word test, trail making, digit span and finger tapping, the modified Mini Mental Status Examination (3MSE) and the modified Rankin scale (MRS). Inclusion criteria were a gait and dementia scale ≥ 12 (range 2-40), a MRS ≥ 2 and a communicating hydrocephalus on CT. Gait disorder and dementia varied from mild to severe leading to MRS 2 in 17%, MRS 3 in 34%, MRS 4 in 21%, MRS 5 in 16% and MRS 6, including akinetic mutism, in 12%. Only one patient showed both normal tandem walking and turning. Small steps, reduced foot floor clearance and wide base were also frequently seen in the 67 patients walking independently; 34 needed assistance or could not walk at all. Applying the 3MSE, 64% was demented; the remaining 36% exhibited a milder cognitive deficit. The 10 word test and trail making decreased with increasing dementia. Digit span and finger tapping declined in the most demented patients. This group of elderly patients with NPH, mostly of the idiopathic type, proved to be vulnerable because of considerable disability and comorbidity.

INTRODUCTION

The Dutch Normal Pressure Hydrocephalus Study is a multicenter randomized study designed to determine the positive and negative predictive value of the resistance to out-flow of cerebrospinal fluid (Rcsf) regarding the results of ventriculoperitoneal shunting in patients with a normal pressure hydrocephalus (NPH). A second objective of the study is to examine whether low or medium pressure shunts are more effective in reversing the signs and symptoms of NPH.

The classical NPH triad consists of a gait disturbance, mental deterioration and urinary incontinence combined with a communicating hydrocephalus on computed tomography.¹ One of the main reasons of the disappointing results of shunting is that the clinical diagnosis of NPH is difficult. Gait disorders, dementia and micturition disturbances occur in many neurological and non-neurological conditions of the elderly. Previous publications often contained retrospectively collected clinical data or the number of patients was small. Having included the required number of patients, we are able to describe here our study protocol, baseline characteristics and clinical findings of a large group prospectively studied NPH patients.

PATIENTS AND METHODS

Clinical and baseline measurements

To quantify the gait disturbance and dementia a gait scale and dementia scale were developed (Table 2.1). The gait scale consisted of a walking, step and time score. Ten features of gait pattern were evaluated for the walking score (Table 2.1a). Tandem walking was classified as disturbed when more than two foot corrections were necessary during eight steps with open eyes. A disturbance of turning was considered to be present when turning was executed with more than two steps. A disturbance of trunk balance was defined as anterior-posterior or lateral sway of the trunk without any foot corrections. For a wide based stride the distance between the feet had to be at least two foot widths. Small steps were present when the distance between the two feet was less than one foot length. The definition of reduced foot-floor clearance was touching the ground with the foot of the swinging leg. Start hesitation was judged to be present when the first steps were slower or smaller than the subsequent ones. Finally, anterior-posterior or lateral foot corrections during walking were noted as a tendency toward falling. For patients unable to walk independently a distinction was made between walking with the assistance of one helper and not being able to walk at all. The number of steps and seconds required for a 10 meter walk of patients walking without help was converted to a step and time score. Adding these to the walking score yielded the gait scale with a range of 2 - 40 points. The dementia scale comprised a short battery of 4 neuropsychological tests (Table 2.1b).

Table 2.1a. Gait scale

Walking score (WS)	
Able to walk independently	
Tandem walking disturbed	2
Turning disturbed	2
Trunk balance disturbed, sway	2
Wide based stride	2
Small steps	2
Reduced foot-floor clearance	2
Start hesitation	2
Tendency toward falling	2
Total	WS = (0-16)
Able to walk with assistance	WS = 18
Not able to walk at all	WS = 20

Number of steps*	Step score (SS)	Number of seconds*	Time score (TS)
<13	1	<10	1
13-15	2	10-11	2
16-18	3	12-13	3
19-21	4	14-15	4
22-25	5	16-18	5
26-29	6	19-21	6
30-33	7	22-24	7
34-38	8	25-27	8
39-43	9	28-30	9
>43	10	>30	10

$$\text{Gait scale}^{**} = \text{WS} + \text{SS} + \text{TS} = \dots(2-40)$$

* Number of steps and seconds required for a 10 meter walk (average of 3 attempts) in patients walking independently

** See Table 2.1b.

Table 2.1b. Dementia scale

Ten Word Test (WT); recall after 5 minutes		Digit Span (DS); sum of forward and reverse		Trail Making (TM); test A		Finger Tapping (FT); 10 sec, average of 3 attempts	
No. of words	WT	No. of figures	DS	No. of seconds	TM	No. of tabs	FT
> 8	1	>11	1	<45	1	>45	1
8	2	11	2	46-60	2	45-41	2
7	3	10	3	61-75	3	40-37	3
6	4	9	4	76-90	4	36-33	4
5	5	8	5	91-105	5	32-29	5
4	6	7	6	106-120	6	28-25	6
3	7	6	7	121-150	7	24-21	7
2	8	5	8	151-180	8	20-17	8
1	9	4	9	181-210	9	16-13	9
0	10	3	10	>210	10	<13	10

$$\text{Dementia scale}^{**} = \text{WT} + \text{DS} + \text{TM} + \text{FT} = \dots(4-40)$$

$$^{**} \text{ NPH SCALE} = \text{GAIT SCALE} + \text{DEMENTIA SCALE}$$

During the 10 word test a list of 10 words was read out loud five times and after each time the patient was asked to recall as many words as possible. The number of words recalled after five minutes is a measure of extended verbal memory. Digit span forwards and backwards provides the immediate verbal memory and attention. Patients were asked to repeat sets of numbers of increasing length in the correct order. Trail making meant the connection of the numbers 1 to 25 written in scattered circles as quickly as possible. Visuospatial performance and psychomotor velocity are determined with this test. Finger tapping for 10 seconds is a simple and reliable method to measure motor velocity. The four test scores were again converted and added in such a way that the resulting dementia scale had the same range as the gait scale. To create one clinical outcome measure, the sum of the gait and dementia scale was referred to as the NPH scale, with a range of 6 to 80 (Table 2.1).

Cognitive disturbances were also recorded with the Modified Mini Mental State Examination (3MSE).¹¹⁸ The modified Rankin scale (MRS) was used as a handicap score to determine general outcome. It was extended to a 7 point scale by inserting MRS grade 4, defined as moderate disability, partial independence, needing assistance for less than

50% of the day. MRS grade 0 or 1 meant no functional disability, grade 2 or 3 mild disability and grade 5 or 6 severe disability.

A lumbar constant flow infusion test^{56;113} was carried out in all patients entering the study. With the patient in lateral recumbent position a 19 Gauge lumbar needle was connected to a pressure monitor and fluid-filled infusion system. The baseline CSF pressure was measured first and after being stable for at least 5 minutes, fluid was infused at a constant rate of 1.4 to 1.6 ml/min until a stable pressure plateau was reached or the pressure rose above 50 mm Hg. In the latter case infusion was repeated at a lower infusion rate. Rcsf is given by the difference between the plateau and the baseline pressure divided by the infusion rate in mmHg/ml/minute.

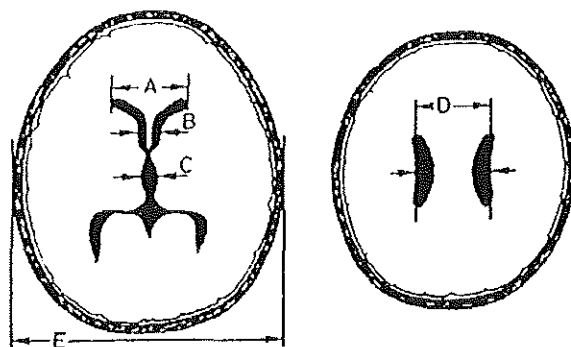
Eligibility

Between September 1990 and July 1995 101 NPH patients enrolled the study in the 4 participating neurological and neurosurgical centers. In establishing the diagnosis of NPH the referring neurologist or neurosurgeon was permitted to use all diagnostic procedures, except continuous recording of intracranial pressure and measurement of Rcsf. After referral to one of the centers, the local study coordinator had to agree with the diagnosis and to verify whether the patient fulfilled the following inclusion criteria:

1. a gradually developed gait disturbance of both legs, unexplained by other conditions and a score of at least 12 on the gait scale.
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 score of at least 2 on the MRS.
4. a CT scan showing a symmetrical communicating quadriventricular hydrocephalus, without clinically relevant parenchymal lesions. Furthermore an Evans' index ≥ 0.3 (maximum width of the frontal horns divided by the maximum inner width of the skull), a ventricular index > 0.8 (sum of maximum width of the anterior horns, width of the anterior horns at the level of the caudate nuclei, maximum width of the third ventricle (3x) and width of the lateral ventricles at the level of the cella media, divided by the greatest external diameter of the skull) and the sum of the 4 largest sulci at the convexity < 25 mm (real size).

We asked for micturition disturbances but they were not an inclusion criterion. Informed consent was given either by the patient or family. Exclusion criteria were acute or subacute symptomatic NPH within 3 months after the causative incident, age of 85 years or more, severe comorbidity with restricted life-expectancy or contraindications for surgery.

Fig. 2.1. Ventricular and skull sizes.



$$\text{Ventricular index} = (A + B + 3C + E) / D$$

All patients were randomized for a low pressure shunt with an opening pressure of 40 ± 10 mm H₂O, or a medium-high pressure shunt with an opening pressure of 100 ± 10 mm H₂O. The gait scale, dementia scale and mRS were determined prior to and 1, 3, 6, 9 and 12 months after operation. CT-scans were obtained preoperative and again 1, 6 and 12 months later. The 3MSE was taken before and 6 and 12 months after shunting. A formal neuropsychological examination using the Wechsler Adult Intelligence and the Wechsler Memory Scales was performed before and 1 year after shunt implantation in 36 patients.

The clinical and CT criteria for shunt failure were: 1) no clinical improvement and no reduction of ventricular size 3 months after operation; 2) clinical deterioration, defined as an increase of 15 % on the NPH scale and a reduction of one grade on the MRS or 3) increase of ventricular size. In all these cases the infusion test was repeated. The shunt was revised if Rcsf was higher than 12 mmHg/ml/min or equal to, or higher than the preoperative Rcsf value. Shunt dysfunctions caused by disposition or disconnection also needed surgical treatment. For patients with proven shunt failure follow up was extended to 12 months after the second operation.

Controls

Ten healthy elderly people, most of them spouses of the patients, were recruited to serve as controls and to rule out any learning effect in the tests of cognitive function. The same schedule as used for the patients was followed, but without CT and spinal infusion test.

RESULTS

Sixty men and 41 women entered the study. Their baseline characteristics are shown in Table 2.2. Except for age, the differences between patients and controls were highly significant ($p < 0.001$). The study contained the whole range of fairly good to fully dependent and immobile patients as reflected in the distribution of MRS scores. Of the 101 patients 17 were classified as MRS 2, 35 as MRS 3, 21 as MRS 4, 16 as MRS 5 and 12 as MRS 6.

Table 2.2. Baseline characteristics of NPH patients and controls

Variable	NPH patients N = 101			Controls N = 10		
	Mean	SD	Range	Mean	SD	Range
Age	73.7	6.3	50 - 85	72.4	4.5	66 - 80
Gait scale	25.6	10.2	12 - 40	5.8	1.9	3 - 10
Dementia scale	23.3	7.6	12 - 40	10.4	3.7	5 - 19
NPH scale	48.8	15.7	27 - 80	16.2	4.8	9 - 26
Modified Rankin scale	3.7	1.3	2 - 6	0.5	0.8	0 - 2
3MSE*	66.2	25.2	0 - 96	94.3	5.0	83 - 100
Length of history	2.3	2.3	0.3 - 1.0			
Evans' index	0.39	0.06	0.3 - 0.55			
Ventricular index	1.19	0.19	0.9 - 1.84			
Baseline pressure [#]	11.2	3.3	5 - 20			
CSF outflow resistance*	17.3	6.3	6.3 - 42.3			

* 3MSE = modified Mini Mental State Examination; [#] in mmHg; * in mmHg/ml/minute

Gait disturbance

Table 2.3 shows that only two-thirds of the patients was able to walk unassisted. Almost all of these patients exhibited disturbed tandem walking and turning. In patients with a mild gait disturbance, equivalent to a gait scale of 12 to 15, two more items were usually present, mostly small steps and reduced foot floor clearance or wide based stride. Their step and time scores were only slightly higher than controls (Fig. 2.1). These patients felt unsafe walking outside, but their gait was not a handicap indoors.

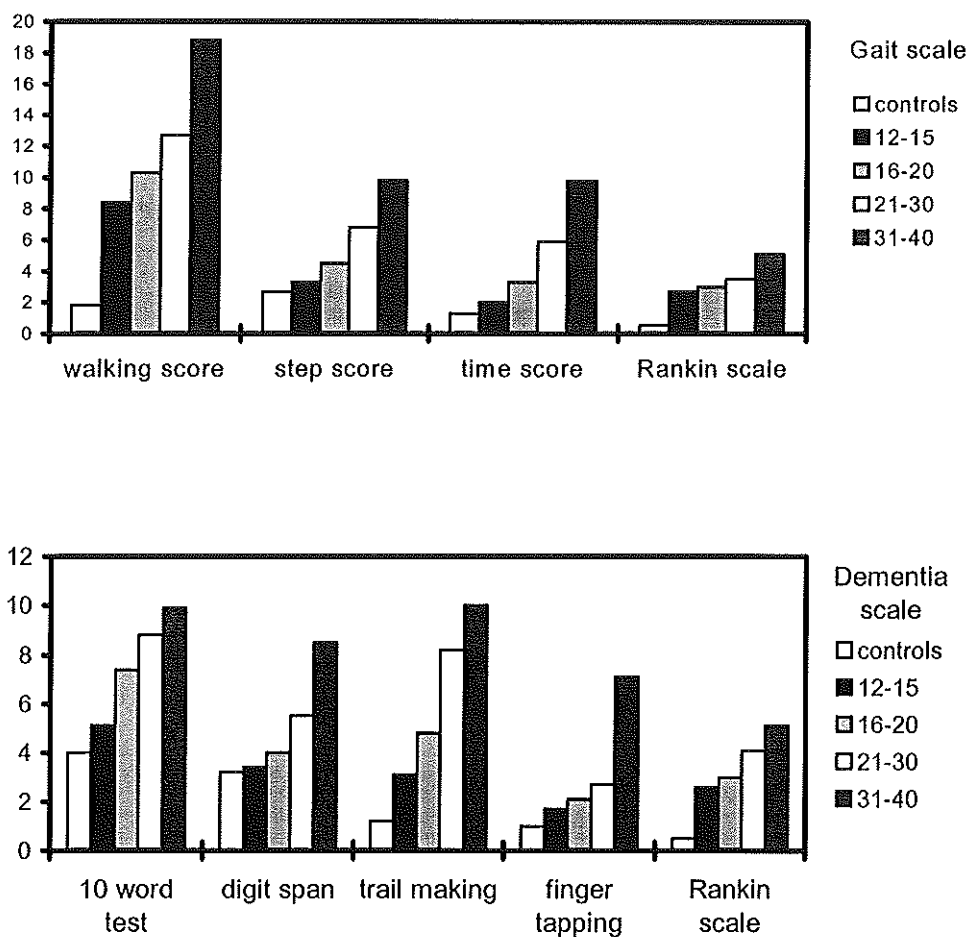
Table 2.3. Gait analysis of NPH patients and controls

	NPH	Controls
<i>Able to walk independently</i>	n = 67	n = 10
Disturbed tandem walking	93%	30%
Disturbed turning	90%	60%
Small steps	82%	0%
Reduced foot-floor clearance	67%	0%
Wide based stride	67%	0%
Tendency toward falling	46%	0%
Disturbed trunk balance, sway	40%	0%
Start hesitation	25%	0%
Mean no. of steps for a 10 m walk	25.7 ± 13.4	15.7 ± 1.3
Mean no. of seconds for a 10 m walk	15.8 ± 9.3	7.8 ± 0.8
<i>Able to walk with assistance</i>	n = 13	n = 0
<i>Not able to walk at all</i>	n = 21	n = 0

If gait was moderately disturbed, gait scale 16 to 20, patients were unable to walk independently outside. The reduction in walking velocity could be partially compensated by a greater number of steps. At higher gait scales the time scores increased more than the step scores, indicating the failing of this compensation mechanism (Fig. 2.1). A walking score of 12 - 14 together with rising step and time scores resulted in a gait scale of 21 - 30. Patients walked indoors with difficulty, outside they needed much assistance or were not able to walk at all. The mean gait scale score at entry of 25.6, therefore, signifies a substantial gait disturbance. Thirteen patients could only walk with assistance, very slowly with very small steps and 21 were not able to walk at all.

The gait analysis of the ten controls was normal except for tandem walking and turning. The difference between controls and NPH patients in terms of the number of steps and seconds required to walk 10 meters was highly significant (both $p < 0.0001$).

In some patients the gait resembled a parkinsonian gait with reduced foot floor clearance and start hesitation. Then a wide based gait favored NPH. Even with a small based gait, the diagnosis of NPH was not rejected, if other parkinsonian features as tremor, hypokinesia and rigidity were absent. Four of our patients were unsuccessfully treated with levodopa preparations. In other patients the main feature of gait was disturbance of trunk balance and a tendency to fall, more resembling a cerebellar syndrome.

Fig. 2.1. Test scores of controls and NPH patients at different gait and dementia scale levels

Other cerebellar signs like nystagmus, ataxia of the limbs and dysarthria, however, were not found. NPH patients tended to fall backwards whereas those with cerebellar ataxia fell to all sides. Ataxia of the trunk while sitting unsupported by legs or trunk was also lacking. Mild pyramidal tract signs also belong to the wide clinical spectrum of NPH. Indeed some patients showed uni- or bilateral Babinski signs but without paresis, hyperreflexia and spasticity. Other causes such as cervical myelopathy were carefully excluded.

Of the 101 patients six presented with a maximum NPH scale of 80 and MRS 6. Although variable, their clinical picture could be described as akinetic mutism. They were

motionless and mute because of a total lack of any drive to action. Fourteen patients had a history of one or more cerebrovascular events, mostly TIAs or minor strokes, without residual neurological deficit. Nerve conduction studies revealed a mild polyneuropathy in nine patients who exhibited diminished or absent ankle jerks without or with minor sensory abnormalities. These conditions might influence neurological function. The gait scale, dementia scale and MRS of these 23 patients were therefore compared with those of the remaining 78 NPH-patients. No difference between the 2 groups could be detected.

Dementia

The cognitive decline is summarized in Table 2.4. The greatest difference between NPH patients and controls was found for the 10 word test. Patients with a dementia scale of 12 - 15 had minor cognitive disturbances and did not give the impression of being demented. Yet their scores on the 10 word test were reduced and they had lost velocity on trail making.

A dementia scale of 16 - 20 was associated with a mild dementia already interfering with independent life. With progression of mental dysfunction the results of the 10 word test and trail making declined (Fig. 2.1). Digit span and finger tapping tended to remain better, but deteriorated in the most demented patients.

Table 2.4. Results of four neuropsychological tests in NPH patients and controls

Variable	NPH patients N = 101		Controls N = 10		p-value
	Mean	SD	Mean	SD	
10 Word Test*	2.2	2.2	6.0	2.5	0.0001
Digit Span					
forward	5.0	1.3	5.7	1.0	0.08
backward	3.0	1.1	4.2	0.9	0.002
total	8.0	2.0	9.9	1.4	0.007
Trail Making, no. of sec	125.5	74.7	55.3	12.6	0.004
Finger Tapping [#]	42.9	11.7	58.0	7.6	0.0001

* no. of words recalled after 5 minutes; [#] no. of taps in 10 sec

The moderately demented patients with a score of 21 - 30 could recall just a few words after 5 minutes and were able to repeat about four digits forward and three backward. The time for trail making showed a threefold increase compared to controls. The mean initial dementia scale score of 23.3 was accompanied by moderate disability, MRS grade 4.

For patients with the most severely disturbed cognitive function, dementia scale 31 - 40, delayed recall after five minutes was nearly zero, trail making was impossible or took too much time and finger tapping went very slowly. The six patients with akinetic mutism could not be tested at all.

The dementia scale scores correlated well with the results of the 3MSE, the coefficient of correlation being -0.88 with a p-value < 0.001.

Micturition - length of history - comorbidity

Although not an inclusion criterion, 83% of the patients had micturition disturbances as well, 35% of whom complained of imperative micturition and 48% of urinary incontinence. The length of history varied from 4 months to 10 years. The symptoms existed for less than one year in 28%, between one and 3 years in 44%, from 3 to 5 in 16% and up to ten years in 12% of the patients. No relationship was discovered between the length of history and severity of the NPH syndrome. The medical history was unremarkable in only nine patients. Much past and present comorbidity was found in the others (Table 2.5). Twenty-six patients presented with one disease and 66 with two or more. Neurological conditions were considered to be the cause of the NPH syndrome in only 12 patients. The remaining 89 patients, including five with head injuries that occurred 13 - 52 years before, were diagnosed as idiopathic NPH.

Ventricular size - Rcsf - opening pressure shunt

Ventricular dilatation was moderate to marked even when the physiological increase of ventricular size in this age group was taken into account (Table 2.2). The values of the Evans' index and ventricular index showed a good correlation. Baseline CSF pressure varied from 5 to 20 mmHg with a mean of 11.2 ± 3.3 mmHg, in agreement with a diagnosis of normal pressure hydrocephalus. A relationship between baseline pressure and Rcsf was lacking in this population. The mean Rcsf of 17.3 mmHg/ml/min was well above the upper limit of normal of 12.0. Seven patients had a clearly normal Rcsf of less than 10, 10 exhibited values in the gray area of 10 - 12 mmHg/ml/min. Linear regression analysis of Rcsf and ventricular index yielded a coefficient of correlation of 0.12, $p=0.22$. No relation was found neither between Rcsf and NPH scale ($r=0.22$, $p=0.02$), nor between ventricular index and NPH scale ($r=0.25$, $p=0.009$).

The opening pressure of the shunt was measured in 28 patients, 14 with a low and 14 with a medium-high pressure shunt. The mean opening pressure for the low group was 40.4 ± 8.7 mm H₂O with a range of 30 - 60, for the medium-high group it was 100.0 ± 15.6 mm H₂O, range 80 - 130. The opening pressure did not correspond to the value given by the manufacturer in eight patients, but in seven this difference was only 5 - 10 and in one 20 mm H₂O.

Table 2.5. Past and concurrent neurological and non-neurological conditions in 101 NPH patients

Neurological	N = 48	Symptomatic*
Cerebrovascular disease	14	1
Polyneuropathy	9	
Head injury	8	3
Epilepsy	5	
Subdural hematoma	4	4
Subarachnoid hemorrhage	3	3
Miscellaneous	5	1
Non-neurological	N = 190	
Cardiovascular	51	
Gastrointestinal	37	
Musculoskeletal	23	
Urogenital	23	
Endocrinological	17	
Respiratory	12	
Miscellaneous	27	

* Symptomatic: number of patients in which condition causes symptomatic NPH

DISCUSSION

When analysing hydrocephalic gait disturbances we firstly have to consider the physiologic changes of gait in the elderly. Gait kinematics were examined in NPH patients, in older patients with gait problems of a different nature and controls of the same age using various kinds of advanced recording equipment.^{31;105;109} Walking velocities and step lengths in controls were found to be remarkably similar to our values. Differences with NPH patients and those with other neurological disorders were highly significant

(Table 2.6). Neurological healthy young and elderly people differ by 20% or less in their kinematic gait measurements.³² Yet elderly people tend to walk slower with smaller steps and they have difficulty with tandem walking and turning.

Table 2.6. Walking velocity and step length in patients with NPH, patients with various neurological diseases and controls

Author	Category	No. of cases	Mean age	Velocity (m/s)	Step length (m)
Elble ³¹	Controls	19	76	0.96	0.54
	Neurological disease	10	79	0.34	0.25
Sørensen ¹⁰⁵	Controls	20	64	1.19	0.49
	NPH	14	60	0.44	0.27
Sudarsky ¹⁰⁹	Controls	6	79	1.13	0.59
	NPH	6	76	0.47	0.30
	Neurological disease	8	79	0.62	0.34
Boon	Controls	10	72	1.15	0.64
	NPH	67*	74	0.63	0.39

* Those 67 of the 101 patients who were able to walk unassisted

All gait disturbances in older persons caused by neurological conditions affecting both legs have common features. Koller et al.⁵⁷ defined a senile gait disorder as the appearance of a broad based gait with small steps, associated with diminished arm swing, stooped posture, flexion of the hips and knees, uncertainty and stiffness in turning, with occasionally start hesitation or a tendency toward falling. Elble et al.³¹ even found a similar gait pattern in patients with vascular dementia, Alzheimer's disease, NPH and peripheral neuropathy, attributable to non-specific reductions of stride.

Sudarsky and Simon,¹⁰⁹ also comparing gait patterns of NPH and other neurological patients, did notice specific abnormalities. NPH patients exhibited a significant drop in number of steps per minute, reduced step height and decreased counter rotation of the shoulders in relation to the pelvis. A decrease in velocity and stride, an increase in sway and the proportion of time spent in double-limb stance were considered to be non-specific features. According to Sørensen et al.¹⁰⁵ hydrocephalic gait was characterized by a very low speed, short steps and ataxia in the vertical direction,

differing from the ataxia in transversal and sagittal directions seen in cerebellar syndromes.

From these kinematic analyses we infer that on the one hand NPH gait has specific abnormalities, the typical wide based, apraxic gait with small steps and feet appearing glued to the floor being present only occasionally. On the other hand NPH gait resembles in many ways the aspecific senile gait disorder with varying pyramidal, extrapyramidal and cerebellar signs. A thorough neurological examination, however, enables the experienced neurologist to exclude many causes of gait disturbances in the elderly and to reach a diagnosis of NPH with some confidence.

In our group of 101 NPH patients only one was able to turn around and walk tandem correctly. We conclude that NPH is a very unlikely diagnosis in such a patient. The reverse is certainly not true, because disturbances of tandem walking and turning are the most frequent and aspecific abnormalities of senile gait.

The cognitive deficit in NPH is considered to be a mild to moderate dementia of the subcortical type. The most important distinction from cortical dementia is the absence of aphasia, apraxia and agnosia. Neuropsychological examination of NPH patients revealed psychomotor slowing, inertia, memory deficits and also diminished visuospatial abilities.^{44;119;131} Our short battery of four bedside neuropsychological tests measures these functions. The 10 word test proved to be the most difficult. Vanneste and Hyman¹³¹ found the same poor delayed recall of verbal information, but when testing recognition of this material the results were better. Their conclusion was that memory storage took place, but that active retrieval of this material was severely disturbed.

The difference between patients and controls was large for trail making as well and trail making declined more rapidly than finger tapping, thereby underlining the importance of diminished visuospatial performance.

The digit span is very suitable for NPH patients, because both immediate verbal recall and auditory attention are evaluated. Since healthy people should be able to repeat 5 - 7 digits forwards the NPH patients with an average of 5 did rather well.¹⁰⁸ Forward and backward digit repetition were separated because the latter is a more complex task, requiring different mental processes in addition to memory.

The number of finger taps of the dominant hand for 10 seconds in the control group fits the average of 55 ± 5 taps given by Strub and Black.¹⁰⁸ Compared to controls the whole group of NPH patients produced significantly less finger taps, but the number of taps remained relatively high, to decline sharply in patients with the highest degree of dementia.

The 3MSE was introduced by Teng and Chui in 1987.¹¹⁸ They added four test items to the Mini Mental State Examination, evaluation of semantic fluency, delayed memory, remote personal information and abstraction. They also introduced a more

graded scoring of the responses and a more standardized testing procedure. This extended the ceiling and the floor of the test, sampled a wider range of cognitive abilities and enhanced the reliability and validity of the scores. Although the 3MSE takes more time than the MMSE, it is still a brief and easy test. The range of the scores increased to zero through 100, with a standard cut-off for impairment of 79. Applying this criterion to the study population 64% of the patients was demented.

The extensive comorbidity implicates that the patients made up a vulnerable group, which indeed developed many further medical problems during the one year of follow up, interfering with the assessment of the results of shunting. Although a restricted life-expectancy or medical conditions, clearly influencing gait or cognitive function, were among the exclusion criteria, some interaction of neurological or non-neurological comorbidity can never be excluded entirely. Orthopaedic problems, such as coxarthrosis or low back pain could worsen a gait disturbance and strokes might contribute to dementia.

The principle pathogenic factor in NPH is thought to be an increase of Rcsf, leading to an increase of ventricular fluid pressure. For the development of hydrocephalus a pressure gradient between ventricle and subarachnoid space must have been present at one time or another. Such a pressure gradient has not been demonstrated convincingly and the mechanism of ventricular dilatation remains somewhat obscure. The CSF outflow disturbance also causes varying reductions of compliance supposedly by compression and then structural alteration of the ventricular wall and periventricular tissue. Furthermore, pre-existing anatomical and biomechanical properties of the brain will affect these processes.

In view of the above it is not surprising that no relation was found between Rcsf on the one hand and ventricular size and severity of clinical signs on the other. The lack of correlation between Rcsf and ventricular volume was already reported by Kosteljanetz and Ingstrup⁵⁹ and Tans and Poortvliet.¹¹⁷ Studies quantifying the clinical signs of NPH, as we did with our NPH scale, are not available in the literature.

In conclusion, the NPH syndrome consists of a wide spectrum of neurological signs and symptoms, varying from a mild gait disturbance with a minor cognitive deficit to an akinetic mutism and from a typical clinical picture with an almost pathognomonic gait pattern and subcortical dementia to an atypical syndrome resembling other conditions associated with abnormalities of gait and cognition. Many previous investigators emphasized that gait disturbances are a prerequisite for NPH. This is further specified by our finding that NPH is a very unlikely diagnosis in patients who can walk tandem and turn round correctly.

**PREDICTION OF OUTCOME AFTER SHUNTING BY RESISTANCE TO OUTFLOW
OF CEREBROSPINAL FLUID**

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ABSTRACT

Object. The authors examined whether measurement of resistance to outflow of cerebrospinal fluid (Rcsf) predicts outcome after shunting for patients with normal-pressure hydrocephalus (NPH).

Methods. In four centers 101 patients (most of whom had idiopathic NPH) who fulfilled strict entry criteria, underwent shunt placement irrespective of their level of Rcsf obtained by lumbar constant flow infusion. Gait disturbance and dementia were quantified by using an NPH scale and the patient's level of disability was assessed by using the modified Rankin scale (mRS). In addition the Modified Mini-Mental State Examination was performed. Patients were assessed preoperative and 1, 3, 6, 9 and 12 months after surgery. Primary outcome measures were based on differences between the preoperative and last NPH scale score and mRS grades. Improvement was defined as a change measuring at least 15% in NPH scale score and at least one mRS grade.

Results. Intention-to-treat analysis of all patients at 1 year yielded improvement for 57% in NPH scale score and 59% in mRS grade. Efficacy analysis, excluding serious events and deaths that were unrelated to NPH, was performed for 95 patients. Improvement rose to 76% in NPH scale score and 69% in mRS grade. Six cut-off levels of Rcsf were related to improvement in the NPH scale score using two-by-two tables. Positive predictive values were approximately 80% for an Rcsf of 10, 12 and 15 mmHg/ml/minute, 92% for an Rcsf of 18 mmHg/ml/minute and 100% for an Rcsf of 24 mmHg/ml/minute. Negative predictive values were low. More important was the highest likelihood ratio of 3.5 for an Rcsf of 18 mmHg/ml/minute. Extensive comorbidity was a major prognostic factor.

Conclusions. Measurement of Rcsf reliably predicts outcome if the limit for shunting is raised to 18 mmHg/ml/minute. At lower Rcsf values the decision depends mainly on the extent to which the clinical and computerized tomography findings are typical of NPH.

INTRODUCTION

After the publication of Katzman and Hussey in 1970⁶⁶ describing a lumbar infusion test, many investigators used measurement of the resistance to outflow of cerebrospinal fluid (Rcsf) in selecting patients with normal-pressure hydrocephalus (NPH) to undergo shunt placement. Whereas the original test was based on constant flow infusion, others developed constant pressure^{19,29} and bolus infusion⁷⁸ techniques. Although good-to-excellent results were obtained using Rcsf as a predictor of outcome,^{19,48,66,75,84,92,113-115} measurement of Rcsf has never become widely accepted, mainly because an equal number of studies yielded low predictive values for improvement after shunt placement.^{26,41,53,60,77,107,135}

Most previous reports, however, suffer from three major limitations. First, the studies were carried out at single institutions by skillful, experienced and dedicated investigators interested in the field of cerebrospinal fluid (CSF) dynamics. The question arises whether the same results will be produced when Rcsf measurements are made in different hospitals by different individuals. Second, the diagnostic characteristics of infusion tests have not been properly evaluated, because patients with NPH underwent shunt placement only when their Rcsf exceeded a certain threshold. Therefore, the negative predictive value of Rcsf is largely unknown. Third, in most studies the number of patients was rather small and outcome measures were not clearly quantified.

We present the results of a multicenter randomized study designed to determine the positive and negative predictive values of Rcsf, obtained by lumbar constant flow infusion, for the outcome of ventriculoperitoneal shunting in patients with NPH. A second objective of this study, comparison of the efficacy of low- and medium-pressure shunts, will be addressed in a separate paper.

CLINICAL MATERIAL AND METHODS

Measurement of gait disturbance and dementia

Gait disturbance was quantified using a gait scale, described in detail elsewhere,¹⁶ that evaluates the presence of 10 features of gait and measures the number of steps and seconds required for a 10-meter walk. Dementia was assessed by using a dementia scale¹⁶ that is composed of the 10-word, digit span forward and backward, trail making and finger tapping tests. To create one neurological outcome measure we added the scores for gait (range 2-40) and dementia (range 4-40) and the totals comprised the NPH scale (range 6-80; Table 3.1). Disturbances in cognition were also evaluated by administration of the Modified Mini-Mental State Examination (3MSE).¹¹⁸ The modified Rankin scale (mRS), used to obtain a disability score, was extended to a 7-point scale by including mRS 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 were enrolled in the study in the four participating neurological and neurosurgical centers. A referring neurologist or neurosurgeon diagnosed each patient as having NPH. After the patient was referred to one of the centers, the local study coordinator had to agree with the diagnosis and to verify that the patient fulfilled the following inclusion criteria:

- 1) a gradually developed gait disturbance of both legs, 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 disability mRS score of at least 2;
- 4) a computerized tomography (CT) scan showing a communicating hydrocephalus with an Evans' index of 0.3 or greater and a ventricular index greater than 0.8,¹⁶ without clinically relevant parenchymal lesions, the sum of the four largest sulci at the convexity being less than 25 mm (real size).

Exclusion criteria included any of the following: acute or subacute symptomatic NPH within 3 months of a causative incident, age of 85 years or more, severe comorbidity with restricted life-expectancy or contraindications for surgery.

Study design

All patients entering the study underwent a lumbar constant flow infusion test.⁵⁶ With the patient placed in the lateral recumbent position a 19 Gauge lumbar needle was connected to a pressure monitor and a fluid-filled infusion system. First, the baseline CSF pressure was measured. Once this pressure remained constant for at least 5 minutes, saline was infused at a constant rate of 1.4 to 1.6 ml/minute until a stable pressure plateau was reached or the pressure exceeded 50 mm Hg. In the latter case infusion was repeated at a lower infusion rate. The Rcsf was calculated as the difference between the plateau and the baseline pressure divided by the infusion rate; the dimension of Rcsf was expressed as mmHg/ml/minute. The infusion tests were carried out in the four participating centers. The recordings were first analyzed by two of the authors (A.J.W.B and J.T.J.T) independently; differences were solved by agreement.

A ventriculoperitoneal Medos Hakim spring-ball valve shunt was placed in each patient, irrespective of the Rcsf value. They were randomized according to whether a low-pressure shunt with a working pressure of 40 ± 10 mm H₂O or a medium-high-pressure shunt with a working pressure of 100 ± 10 mm H₂O was used. The gait scale, dementia scale and mRS values were determined before and 1, 3, 6, 9 and 12 months after surgery. The 3MSE was administered before and 6 and 12 months after

shunt placement. Computerized tomography scans were obtained preoperatively and again after 1, 6 and 12 months.

The clinical and CT criteria for suspicion of shunt failure were: 1) no clinical improvement and no reduction in ventricular size 3 months after surgery; 2) clinical deterioration, defined as an increase of 15% in NPH scale score and a reduction of one mRS grade or 3) increase in ventricular size. In these cases the infusion test was repeated. The shunt was revised if the Rcsf was higher than 12 mmHg/ml/minute or equal to or higher than the preoperative Rcsf value. Shunt dysfunctions caused by a shift in position or by disconnection also were surgically treated. For patients with proven shunt failure, follow-up evaluation took place 12 months from the last operation.

Control group

Ten healthy elderly people, most of them spouses of the patients, were recruited to serve as controls and to study possible learning effects of the tests of cognitive function. The follow-up schedule was the same as that used in the patients but did not include CT scanning or the lumbar infusion test.

Outcome measures

The differences between preoperative and last NPH scale scores and mRS grades were designated as the primary outcome measures (Table 3.1). Because it proved easier to measure improvement starting at a high rather than low level of the NPH

Table 3.1. Calculation of outcome measures used in the Dutch NPH study

Scale	Range	Calculation of outcome measure	
Gait	2 - 40	$\frac{\text{preop score} - \text{last}^* \text{ or mean}^* \text{ follow-up score}}{\text{preop score}}$	x 100
Dementia	4 - 40	$\frac{\text{preop score} - \text{last}^* \text{ or mean}^* \text{ follow-up score}}{\text{preop score}}$	x 100
NPH [†]	6 - 80	$\frac{\text{preop score} - \text{last}^{\#} \text{ or mean}^* \text{ follow-up score}}{\text{preop score}}$	x 100
mRS	0 - 6	preop grade - last [#] or mean* follow-up grade	
3MSE	0 - 100	preop 3MSE - 6* or 12* mo 3MSE score	

* Secondary outcome measures; [#] primary outcome measures.

[†] The NPH scale is composed of the sum of the gait scale and dementia scale.

scale, the changes in NPH scale score were expressed as a percentage of the preoperative value. For instance, for NPH scale scores of 60 at study entry and 45 at 12 months, improvement was calculated as $[(60-45)/60] \times 100 = 25\%$. The more even distribution of disability between the mRS grades justified the use of numerical grade differences. Using the primary outcome measures improvement was classified as none, moderate, marked or excellent (Table 3.2). Any improvement was defined as a change between the entry and the last score that measured at least 15% of the NPH scale score and one grade in the mRS.

Secondary outcome measures included the differences between preoperative and the mean of the follow-up NPH scale scores and mRS grades as well as improvement in gait scale, dementia scale and 3MSE values (Table 3.1).

Table 3.2. Classification of improvement in Dutch Normal-Pressure Hydrocephalus Study

Level of improvement	Improvement in NPH scale score (%)	Improvement in modified Rankin scale (grades)
None	< 15	< 1
Moderate	15-29	1
Marked	30-44	2
Excellent	≥ 45	≥ 3

Intention-to-treat and efficacy analyses

Intention-to-treat analysis of the results of shunt placement was performed for all 101 patients by using all available outcome information. The main outcome was expressed as the proportion of patients who improved 12 months after surgery. The 15 deaths and the one patient lost to follow-up were categorized as unimproved.

The relationship between Rcsf and outcome after shunt placement was studied by means of efficacy analysis. To assess more accurately the results of shunt placement in the 95 patients who could be evaluated, all known serious events that were unrelated to NPH and clearly interfered with neurological function were excluded. The deaths of the aforementioned 10 patients and another 17 events (such as stroke, severe cardiac failure and hip fracture) were recorded and the results from the last follow-up examination before the event were used to calculate the outcome measure.

The efficacy analysis consisted of two parts. The Rcsf values were correlated with primary and secondary outcome measures by using linear regression analysis. For the second part of the analysis, the proportion of patients exhibiting improvement according to the primary outcome measures (Table 3.2) was related to different levels of Rcsf using two-by-two tables.

RESULTS

Baseline characteristics

Sixty men and 41 women entered the study. Their baseline characteristics are shown in Table 3.3. The study cohort covered the whole range of fairly good to fully dependent and immobile patients, as reflected in the distribution of mRS grades at entry. Of the

Table 3.3. Baseline characteristics in 101 patients with NPH

Variable	Mean \pm SD*	Range
Age (yrs)	73.7 \pm 6.3	50 - 85
Duration of history (yrs)	2.3 \pm 2.3	0.3 - 10
Gait scale score	25.6 \pm 10.2	12 - 40
Dementia scale score	23.3 \pm 7.6	12 - 40
NPH scale score	48.8 \pm 15.7	27 - 80
mRS grade	3.7 \pm 1.3	2 - 6
3MSE score	66.2 \pm 25.2	0 - 96
Evans' index	0.39 \pm 0.06	0.3 - 0.55
Ventricular index	1.19 \pm 0.19	0.9 - 1.84
Baseline CSF pressure (mmHg)	11.2 \pm 3.3	5 - 20
Rcsf (mm/Hg/ml/minute)	17.3 \pm 6.3	6.3 - 42.3

* SD = standard deviation

101 patients, 17 were classified as mRS grade 2, 35 as grade 3, 21 as grade 4, 16 as 5 and 12 as grade 6. The mean gait score of 25.6 at entry signified a substantial gait disturbance. Only two-thirds of our patients were able to walk unassisted. The mean initial dementia score of 23.3 indicated a moderate dementia clearly interfering with independent life. With a cutoff score of 79 for dementia, the mean 3MSE score of 66.3 also pointed to moderate dementia. No less than six patients presented with the clinical picture of akinetic mutism. The extensive rate of comorbidity with 48 past and con-

comitant neurological and 190 non-neurological conditions further underlined the rather severe disabilities suffered by our patient population.¹⁶

The distribution of Rcsf values is shown in Table 3.4. Taking 12 mmHg/ml/minute as the upper limit of a normal Rcsf, 83% of patients showed increased Rcsf, indeed demonstrating the presence of a disturbance in CSF absorption in the majority of the study population.

Control group

The 10 control patients did not show gait and cognitive disturbances at entry. The gait and dementia scales and 3MSE scores revealed no significant or systematic changes over follow-up period; any learning effect for the scoring of these tests is, therefore, unlikely.

Outcome after shunt placement

In view of the course of NPH scale scores found in the 95 patients who could be evaluated, four patterns were recognized. For half of the patients, most of the improvement took place in the first month and remained stable from that time onwards. Approximately one-quarter of the patients never showed improvement: their scores remained more or less the same from the beginning. The NPH scale scores decreased initially and increased at a later stage or exhibited a steady decrease in the remaining patients.

Separate evaluation of changes in gait and cognitive function revealed that gait improved more than 40% and dementia less than 20% (Table 3.5). The rate of improvement, however, was the same. The small differences between the final follow-up evaluation and the mean of all follow-up evaluations indicate that the last NPH scale and mRS values reliably reflect the results of shunt placement. The average increase of 10 points in the 3MSE score at 6 as well as 12 months also points to early improvement in cognition. Taken as a percentage of the mean score at study entry, the improvement in the 3MSE score was less than that in the dementia scale. The mean reduction in the mRS was one grade.

According to the intention-to-treat analysis of all 101 patients with NPH, 57% showed improvement in the NPH scale score and 59% improvement in mRS after 1 year of follow-up. A marked-to-excellent result after shunt placement was found for 41% of the NPH scale scores and 34% of the mRS grades.

Table 3.4. Relation of Rcsf to outcome measured as improvement in NPH scale score and mRS grade on the basis of efficacy analysis in 95 patients with NPH*

IMPROVEMENT (no. of cases)									
Rcsf	Total no. of cases	NPH scale				Modified Rankin scale			
		None	Mod	Mark	Exc	None	Mod	Mark	Exc
< 10	6	3	1	1	1	2	1	1	2
10 - 11.9	10	5	1	0	4	4	3	2	1
12 - 14.9	14	2	3	2	7	2	5	5	2
15 - 17.9	29	10	6	7	6	15	8	4	2
18 - 20.9	15	0	6	5	4	1	6	5	3
21 - 23.9	11	3	2	3	3	5	4	1	1
≥ 24	10	0	2	4	4	0	3	4	3
Totals	95	23	21	22	29	29	30	22	14

* See Table 2 for classification of improvement. Abbreviations: Exc = excellent; Mod = moderate; Mark = marked

Relation of Rcsf to outcome

The positive and negative predictive values of Rcsf were investigated by means of efficacy analysis after exclusion of events unrelated to NPH. Linear regression analysis of Rcsf compared with the primary and secondary outcome measures revealed that all correlations were weak (Table 3.5). Evaluation of the plots of these data showed that these correlations were not influenced by shunt type and that the existence of nonlinear relationships could be excluded as well. The degree of the CSF absorption deficit, as quantified by our Rcsf measurements, obviously does not agree with the degree of clinical improvement after a shunt operation.

Shunt placement resulted in a meaningful improvement in gait and cognition measuring 15% or greater for 75% of the 95 patients and an advance of at least one grade in the mRS for 69% of them (Table 3.4). In the group of patients with an Rcsf lower than 12 mmHg/ml/minute, 63% of those who did not exhibit improvement developed comorbidity that adversely affected their activities of daily life during the follow-up period compared with none of those who experienced improvement ($p=0.03$). A similar difference was found for Rcsf greater than 12 mmHg/ml/minute with comorbidity emerging in 67% of patients without and 20% with improvement ($p=0.001$). A

substantial portion of this comorbidity was intracranial and extracranial vascular disease. Unimproved patients also presented more often with a history of ischemic heart and/or peripheral vascular disease, indicating that comorbidity in general and vascular diseases in particular are detrimental to the results of shunting.

Table 3.5. Linear regression analysis of Rcsf versus all outcome measures on the basis of efficacy analysis in 95 patients with NPH*

Outcome measure	Mean \pm SD (%)	Correlation with Rcsf	
		r value	p value
last gait scale score	41.2 \pm 28.8	0.17	0.10
mean gait scale score	38.0 \pm 28.0	0.20	0.06
last dementia scale score	18.9 \pm 20.5	0.25	0.01
mean dementia scale score	15.3 \pm 18.9	0.25	0.02
last NPH scale score	30.7 \pm 21.5	0.21	0.04
mean NPH scale score	27.5 \pm 20.6	0.22	0.03
last mRS grade	1.2 \pm 1.2	0.16	0.11
mean mRS grade	1.0 \pm 1.1	0.21	0.04
3MSE score at 6 mos	8.2 \pm 17.9	0.01	0.95
3MSE score at 12 mos	9.9 \pm 18.1	0.02	0.88

* See Table 3.1 for calculations of outcome measures. Abbreviations:
SD = standard deviation

Using improvement in NPH scale score after shunt placement as the criterion for diagnosis of NPH, the pretest probability of an Rcsf \geq 12 mmHg/ml/minute was 76% and the positive predictive value 81% (Table 3.6). The latter was comparable for Rcsf values of 10 and 15 mmHg/ml/minute and rose to 92% for an Rcsf of 18 mmHg/ml/minute and 100% for an Rcsf of 24 mmHg/ml/minute. Because of the considerable number of patients who improved despite a negative test, the negative predictive values were low. Sensitivity decreased and specificity increased with rising

Rcsf values. The highest likelihood ratio (sensitivity/1-specificity) by far was found at a Rcsf cut-off of 18 mmHg/ml/minute (Table 3.6).

DISCUSSION

The Dutch Normal Pressure Hydrocephalus Study is the first large prospective trial in which all patients underwent shunt placement, independent of Rcsf level, and all patients were systematically and quantitatively evaluated before and after shunting.

We have developed an NPH scale to measure gait disturbance and dementia. By assigning the same weight to the two scales and by ensuring that there was agreement in severity of signs and scores between the two scales, we considered it justifiable to add the gait and dementia scores to create one outcome measure. The almost equal mean gait and dementia scale scores at entry indicate that our goal was achieved. The translation of the various scores of the NPH scale into a clinical picture is described extensively elsewhere.¹⁶

Table 3.6. Predictive values for any improvement at different cutoffs of Rcsf on the basis of efficacy analysis in 95 patients with NPH by using improvement in NPH scale score as the outcome measure*

Cutoff Rcsf (mmHg/ml/min)	Sensitivity (%)	Specificity (%)	Likelihood ratio	Positive predictive value (%)	Negative predictive value (%)
10	96	13	1.1	78	50
12	89	35	1.4	81	50
15	72	44	1.3	80	33
18	46	87	3.5	92	34
21	25	87	1.9	86	27
24	14	100	∞	100	27

* See Table 3.2 for classification of improvement. Abbreviations: neg = negative; pos = positive

Teng and Chui¹¹⁸ extended the Mini-Mental State Examination³³ (MMSE) to the 3MSE by adding an evaluation of semantic fluency, delayed memory, remote personal information and abstraction. We consider the 3MSE to be a very valuable addition to the evaluation of patients with NPH. The 3MSE takes only 15 minutes to administer

and provides better and more cognitive information than the MMSE. Comparison of the MMSE and the 3MSE in a stroke population revealed that better results were obtained using the 3MSE.³⁸

Outcome after shunt placement

When judging the results of shunting in these elderly patients, we have to take their vulnerable constitution into account. Two-thirds of the patients had at least two other past or present diseases, 28% were severely handicapped at entry and 15 patients died of conditions unrelated to NPH during the 12 months of follow-up review.

Most of our patients suffered from idiopathic NPH and some from a chronic symptomatic NPH. The improvement rate of 59% 1 year after shunt placement compares well with previous findings. In a series of 64 patients with a higher percentage of symptomatic NPH, 58% showed improvement at one year.¹⁸ The duration of follow-up seems to be an important factor. An improvement of 42% at 2 years was reported in 45 patients with idiopathic NPH,³⁰ whereas 70% of 37 patients showed improvement 2 months after surgery.¹⁰ Outcome is also influenced considerably by the inclusion or exclusion of morbidity and mortality factors unrelated to NPH. When all events were included, a success rate of 37% was calculated;⁴² when unrelated events were excluded, it was 69% according to the mRS, 76% using our NPH scale and 78% in the study conducted by Larsson, and colleagues.⁶⁹ Black¹¹ mentioned that marked improvement is seen in only 20 to 30% of cases in most series. Such an improvement, equivalent to an advance of at least 2 grades of the mRS, was recorded for 34% of patients in our study.

Among patients who improved, most changes took place in the first month. Contrary to what is generally accepted, the same rate of improvement was found for gait and cognitive disturbances. The degree of improvement in gait, however, was twice as high.

In most cases of unsuccessful shunt placement, the patients did not show improvement at any of the follow-up visits. Treatment failure in this group was presumably due to excessive, mainly vascular, comorbidity leading to irreversibility of the NPH syndrome. Emerging comorbidity may have also caused deterioration of patients who exhibited initial improvement. Such a course has been reported by others.^{10;11;18} Shunt failure would have been detected because of the strict protocol definitions; however, subdural effusions may have affected outcome.

The duration of disease correlated with outcome in some studies^{39,90} but not in that of Börgesen¹⁹ or in ours. Our entry criteria, allowing only enrollment of patients with dementia which started together with or after the gait disturbance, make it impossible to

confirm that the occurrence of gait abnormalities prior to dementia is a favorable prognostic sign.³⁹

Cerebrospinal fluid outflow resistance

Determination of Rcsf can be accomplished by constant flow, constant pressure and bolus infusion techniques. It has been demonstrated convincingly that an Rcsf obtained from bolus infusions is lower than the Rcsf calculated by constant flow infusion and that this discrepancy increases with increasing Rcsf.^{59;110;111;115} The constant pressure infusion methods are attractive because, by using them, more data can be obtained during a given time period than with a constant flow infusion.^{19;29} Distinct disadvantages are the more invasive nature of the procedure (two punctures of the CSF space) and the more complicated equipment required. We favor using simple lumbar constant flow infusion with one or two infusion rates which has proved to be a reliable and reproducible method in our hands.^{113;115} In this study the investigators from the four centers encountered problems performing the infusion test in only one case.

The Rcsf was measured in young volunteers³ and in patients suspected of altered hydrodynamics who ultimately proved to have no neurological disease.³⁰ In both studies, the authors reported an upper limit of normal of 10 mmHg/ml/minute, with mean values of 9 and 6.9 mmHg/ml/minute, respectively.

Cerebrospinal fluid outflow resistance related to outcome

At the simplest level a CSF absorption deficit is assumed to cause an increase in CSF pressure and ventricular dilatation that leads, by whatever mechanisms, to the signs and symptoms of NPH. Because no relationships have been found between CSF pressure and ventricular size, on the one hand, and severity of the NPH syndrome before and after shunt placement, on the other,^{18;90;116} it is not surprising that no correlation could be found between Rcsf and changes in NPH scale, 3MSE or mRS values after surgery.

The main objective of this study was to determine the positive and negative predictive values of Rcsf. There is no consensus on the level of Rcsf above which patients should undergo shunt placement. Various investigators have used 8¹⁹, 10^{30;41}, 12^{26;75}, 13¹¹⁶ and 15⁹² mmHg/ml/minute as their threshold. The design of this study, in which all patients underwent shunt placement irrespective of their Rcsf, offers the opportunity to define that limit more clearly. At cutoff values 10, 12 and 15 mmHg/ml/minute, positive predictive values for improvement in gait and cognition were approximately 80%, but the likelihood ratios were low. The likelihood ratio rose to 3.5, accompanied by a positive predictive value of 92%, for Rcsf 18 mmHg/ml/minute. The negative predictive values were disappointingly low for all levels of Rcsf. Using a cutoff

of 12.5 mmHg/ml/minute, Börgesen¹⁸ reported a positive predictive value of 84% and a negative value of 100%. These better results are partially explained by the fact that 20% of the patients with a Rcsf less than 8.3 mmHg/ml/minute did not undergo shunt placement. Other investigators have also declared Rcsf a reliable predictor of outcome.^{48;66;75;115}

On the other hand, a number of authors did not find measurement of Rcsf useful for the selection of NPH patients to undergo shunt placement.^{26;41;53;60;77} The study by Kosteljanetz and colleagues⁶⁰ consisted of only 14 patients and the unreliable bolus infusion method was used. In a study of 35 patients with idiopathic NPH, follow-up lasted only 3 months⁷⁷ and in the study by Delwel, et al.,²⁶ Rcsf was used as a criterion for the diagnosis of NPH.

Price⁹² is one of the few researchers who emphasized the importance of different cutoff levels of Rcsf. The proportion of his patients responding positively to shunt placement increased almost linearly with increasing Rcsf. Patients with an Rcsf of 15 to 18 mmHg/ml/minute did not improve; in contrast the response rate was at least 75% for Rcsf values above 30 mmHg/ml/minute. Although our patients improved with lower Rcsf values, we are able to confirm his findings. We propose that the Rcsf limit for shunting should be raised from approximately 12 to 18 mmHg/ml/minute. If we had used that criterion 33 patients would have benefited at the expense of 3 who did not. Patients with an Rcsf below 18 mmHg/ml/minute and the combination of clinical as well as CT findings that are truly typical for NPH should undergo shunt placement. Otherwise the patients might be followed using quantitative evaluation.

How do we explain the good results of shunt placement in patients with a low Rcsf? Marked leakage around the needle during an infusion test is easily detected. Some leakage at higher pressures is difficult to exclude but does not explain the low Rcsf. Another possibility is that the physiological variability of Rcsf is greater than previously assumed. An Rcsf of approximately 10 mmHg/ml/minute might lead to the signs and symptoms of NPH in some patients.

More important is the problem of patients who did not improve despite an increased Rcsf. The diagnosis of NPH remains difficult.¹⁶ Although our entry criteria were strict, some patients developed progressive dementia with aphasia during follow-up period. Of concern was the frequent occurrence of extracranial and intracranial vascular diseases. Larsson and colleagues,⁶⁹ who identified a group of patients with NPH caused by cerebrovascular disease, reported that outcome for this group was worse than that for patients with idiopathic NPH. Further evidence that these patients are less responsive to shunt placement is provided by a transcranial Doppler study that showed a worse prognosis for patients with arterial stenosis.³⁴

Does every NPH patient need an infusion test? Selection of patients for shunt placement on clinical grounds only is difficult. If Rcsf is less than 18 mmHg/ml/minute, it is useful to know the presurgical level of Rcsf to diagnose shunt dysfunction later. Also, baseline pressure and the amplitude of arterial pulsations might provide additional information. Finally, the principal pathogenic factor of NPH is an increase in Rcsf; therefore, Rcsf measurement should advance our understanding of this condition.

In conclusion, when deciding to place a shunt in a patient with NPH, it must be kept in mind that only one-third will improve markedly and 60% will experience worthwhile improvement after 1 year, a percentage which will drop in the following years. Comorbidity with an emphasis on vascular disease is an important prognostic factor for this age group. The Rcsf obtained by means of lumbar constant flow infusion is a reliable tool for the selection of patients to undergo shunt placement if the Rcsf limit is raised to 18 mmHg/ml/minute. For lower Rcsf values patients should undergo shunt placement when pathognomonic clinical and CT features of NPH are present.

RANDOMIZED COMPARISON OF LOW AND MEDIUM PRESSURE SHUNTS

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ABSTRACT

Object. The goal of this prospective study was to compare outcome after placement of a low- or medium-pressure shunt in patients with normal-pressure hydrocephalus (NPH).

Methods. Ninety-six patients with NPH were randomized to receive a low-pressure ventriculoperitoneal shunt (LPV; 40 ± 10 mmH₂O) or medium-high-pressure ventriculoperitoneal shunt (MPV; 100 ± 10 mmH₂O). The patients' gait disturbance and dementia were quantified by applying an NPH scale and their level of disability was evaluated by using the modified Rankin scale (mRS). Patients were examined prior to and 1, 3, 6, 9 and 12 months after surgery. Primary outcome measures were determined by differences between the preoperative and last NPH scale scores and mRS grades. The LPV and MPV shunt groups were compared by calculating both the differences between mean improvement and the proportions of patients showing improvement.

Results. Intention-to-treat analysis of mRS grades yielded a mean improvement of 1.27 ± 1.41 for patients with LPV shunts and 0.68 ± 1.58 for patients with MPV shunts ($p=0.06$). Improvement was found in 74% of patients with LPV shunts and in 53% of patients with MPV shunts ($p=0.06$) and a marked-to-excellent improvement in 45% of patients with LPV shunts and 28% of patients with MPV shunts ($p=0.12$). All outcome measures indicated trends in favor of the LPV shunt group, with only the dementia scale reaching significance. After exclusion of serious events and deaths unrelated to NPH, efficacy analysis showed the advantage of LPV shunts to be diminished. Reduction in ventricular size was also significantly greater for patients in the LPV shunt group ($p=0.009$). Subdural effusions occurred in 71% of patients with an LPV shunt and in 34% with an MPV shunt; however, their influence on patient outcome was limited.

Conclusions. Outcome was better for patients who had an LPV shunt than for those with an MPV shunt, although most differences were not statistically significant. The authors advise that patients with NPH be treated with an LPV shunt.

INTRODUCTION

Thirty-two years after the first description of normal pressure hydrocephalus (NPH),^{1,46} selection of the opening, closing, or, more appropriately, working pressure of shunts is a matter of continuing controversy. In most larger studies medium pressure shunts were used.^{11;18;41;53} In others low pressure^{76;97} or high pressure^{10;68} valves were preferred. Many investigators inserted shunts of various working pressures without reporting the criteria for their choice or without comparing their efficacy.^{42;49;69;90;106} Vanneste, et al.,¹²⁹ did not find any differences between the various working pressures. McQuarrie and colleagues⁸⁰ obtained better results with low-pressure than medium pressure shunts in a retrospective study of 72 patients who had NPH. In contrast, in the study conducted by Larsson, and associates,⁶⁸ 13 patients improved with programmable shunts set at a high pressure without further improvement at medium- and low-pressure settings.

Surprisingly enough, randomised trials have never been performed. An aim of the multicenter, randomized Dutch Normal-Pressure Hydrocephalus Study was to examine whether low- or medium-pressure shunts are more effective in reversing the signs and symptoms of NPH. The second objective, determination of the predictive value of the resistance to outflow of cerebrospinal fluid (Rcsf) for the outcome after shunting, has been dealt with elsewhere.¹⁴

CLINICAL MATERIAL AND METHODS

Measurement of gait disturbance and dementia

Gait disturbance was quantified by using a gait scale, described in detail elsewhere,¹⁶ to evaluate the presence of 10 features of gait and to measure the number of steps and seconds required for a 10-meter walk. Dementia was assessed by a dementia scale that is composed of the 10-word, digit span forward and backward, trail making and finger tapping tests. To create a single neurological outcome measure, we added the scores for gait (range 2-40) and dementia (range 4-40) and the totals comprised the NPH scale (range 6-80). The modified Rankin scale (mRS), used to obtain a disability grade, was extended to a 7-point scale by inserting mRS grade 4 (defined as moderate disability, partially independent and needing assistance for < 50% of the day).

Eligibility Criteria

Between September 1990 and July 1995 101 NPH patients were enrolled in the study because they fulfilled the following inclusion criteria: 1) a gradually developed gait disturbance in both legs, unexplained by other conditions and a gait scale score of at least 12; 2) a mild-to-moderate cognitive deficit without aphasia, emerging with or after the gait disturbance and a dementia scale score of at least 12; 3) a disability mRS grade of

at least 2; and 4) a computerized tomography (CT) scan showing communicating hydrocephalus with an Evans' index of 0.3 or greater and a ventricular index > 0.8 ,¹⁶ without clinically relevant parenchymal lesions, the sum of the four largest sulci at the convexity being less than 25 mm (real size).

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

Study design

All patients in the study underwent a lumbar constant flow infusion test⁵⁶ and a Medos Hakim spring-ball valve shunt (Johnson & Johnson Medos S.A., Le Locle, Switzerland) was placed in each patient, irrespective of the Rcsf value. The working pressure of the valve was measured just before implantation in 28 of our patients. The patients were randomized to a low pressure ventriculoperitoneal shunt (LPV; 40 ± 10 mm H₂O) or a medium-high pressure ventriculoperitoneal shunt (MPV; 100 ± 10 mm H₂O). Randomization was maintained by telephone communication between the local co-ordinator and the study center. Shunts were allocated to patients according to the randomization lists prepared for each of the four centers separately. The gait and dementia scale scores and the mRS grades were determined prior to and 1, 3, 6, 9 and 12 months after surgery. Computerized tomography scans were obtained preoperatively and after 1, 6 and 12 months postoperatively.

Clinical and CT findings that raised suspicion of shunt failure included any of the following: 1) no clinical improvement and no reduction in ventricular size 3 months after surgery; 2) clinical deterioration, defined as an increase of 15% in the NPH scale and a reduction of one grade in the mRS; or 3) increase in ventricular size. In these cases the infusion test was repeated. The shunt was revised if the Rcsf was found to exceed 12 mmHg/ml/min or if the Rcsf value was equal to or higher than the preoperative Rcsf value. Shunt dysfunctions caused by displacement or disconnection also required surgical treatment. For patients with proven shunt failure, follow up extended 12 months after the last operation.

Outcome Measures

Primary outcome measures were determined by the differences between the preoperative and either the last NPH scale scores and mRS grades. Because it proved easier to measure improvement by starting at a high rather than low level of the NPH scale, changes in the NPH scale score were expressed as a percentage of the preoperative value. For instance, for NPH scale scores of 60 at study entry and of 45 at 12 months, improvement was calculated as $[(60-45)/60] \times 100 = 25\%$. The more even

distribution of disabilities across mRS grades justified the use of numerical grade differences. Secondary outcome measures were determined by the differences between preoperative NPH scale scores and mRS grades and the means of the follow-up scores and grades as well as changes in gait and dementia scale scores. Improvement was classified using primary outcome measures (Table 4.1).

Table 4.1. Classification of improvement in Dutch Normal-Pressure Hydrocephalus Study

Level of improvement	Improvement in NPH scale score (%) [*]	Improvement in modified Rankin scale (grades)
None	< 15	< 1
Moderate	15-29	1
Marked	30-44	2
Excellent	≥ 45	≥ 3

^{*} NPH scale score + gait scale + dementia scale score

Follow-up evaluation

Of the 101 patients five died of diseases that were unrelated to the shunt before the first follow-up examination at one month. Causes of death included stroke, cardiac failure, mesenteric arterial thrombosis, pneumonia and head injury. Therefore, shunt working pressure could be correlated with outcome for 96 patients. Eleven patients, five in the LPV and six in the MPV shunt group, died during the follow-up period as a result of pneumonia (three patients), cardiac failure (two patients), stroke (two patients), peritonitis (one patient) and unknown causes (three patients). One patient was lost to follow-up after 3 months because he returned to his native country, leaving 84 patients for whom complete 12 month follow-up data were available. The mean follow-up periods were 10.9 ± 3.1 months in the LPV shunt group and 10.7 ± 3.2 months in the MPV shunt group.

Intention-to-treat and efficacy analysis

The results of shunt placement were studied by comparing the means of primary and secondary outcome measures for the 49 patients in the LPV shunt group and the 47 patients in the MPV shunt group by using Student's t-test. The proportions of patients

who exhibited improvement were compared between both groups by using the chi-square test.

Intention-to-treat analysis was performed using all available outcome information at 12 months or the last follow-up examination. The 11 patients who died and the patient who was lost to follow-up were categorized as unimproved. For efficacy analysis, all known serious events that were unrelated to NPH and clearly interfered with neurological function were excluded. Thus for the 11 patients who died and another 17 patients who suffered clinically significant events, such as stroke or hip fracture, the results of the last follow-up examination performed before this event were used to calculate the outcome measure. Twelve of these events occurred in the MPV shunt group and five in the LPV shunt group.

Table 4.2. Baseline characteristics in 96 patients with NPH randomized to LPV and MPV groups*

Characteristic	LPV group (49 patients)	MPV group (47 patients)
Age (yrs)	73.7 ± 6.1	73.7 ± 6.8
Duration of symptoms (yrs)	2.2 ± 2.5	2.3 ± 2.2
Gait scale score	24.5 ± 9.8	26.3 ± 10.4
Dementia scale score	23.2 ± 7.7	23.0 ± 7.3
NPH scale score	47.6 ± 16.1	49.2 ± 14.7
mRS grade	3.7 ± 1.3	3.7 ± 1.2
Ventricular index	1.18 ± 0.15	1.22 ± 0.17
Evans' index	0.38 ± 0.04	0.39 ± 0.05
Rcsf (mmHg/ml/minute)	17.8 ± 6.8	17.3 ± 5.4
Baseline pressure (mmHg)	10.6 ± 4.1	10.9 ± 3.7

* Values are expressed as the mean ± standard deviation.

Complications and ventricular size

Any accumulation of subdural fluid, however small, that was seen on a follow-up CT scan was recorded as a subdural effusion (SDE). The number of patients in whom an SDE was revealed and the influence of SDE on outcome were compared in the LPV and MPV shunt groups. All other complications of shunt placement were carefully

recorded. Reduction in ventricular size was expressed as the reduction rate, which was calculated by dividing the preoperative ventricular index by the ventricular index measured on the last follow-up CT scan.

RESULTS

The 96 patients who could be evaluated - 55 men and 41 women - were adequately randomized across the LPV and MPV shunt groups (Table 4.2). Eleven patients had chronic symptomatic NPH (seven in the LPV shunt group and four in the MPV shunt group); the remaining 85 cases were idiopathic.

Working pressure of the shunt

The working pressure of the shunt was measured in 28 cases, 14 of whom had an MPV shunt. The mean working pressure for patients in the LPV shunt group was 40.4 ± 8.7 mm H₂O with a range of 30 to 60 mm H₂O; that for patients in the MPV shunt group was 100.0 ± 15.6 mm H₂O, range 80 to 130 mm H₂O. Opening pressure did not correspond to the value specified by the manufacturer in eight cases; however, in seven of these cases this difference was only 5 to 10 mm H₂O and in one case it was 20 mm H₂O.

Outcome after shunt placement

Intention to treat analysis revealed clinically relevant differences in outcome after 1 year between patients in the LPV and MPV shunt groups (Table 4.3). The last dementia scale scores were significantly better for patients in the LPV shunt group and the last mRS grades came close to significance. Efficacy analysis yielded smaller differences between the two groups because of the exclusion of deaths and invalidating events unrelated to NPH, which occurred more frequently in the MPV shunt group.

Primary outcome measures were used to calculate the proportion of individuals in both groups who responded to shunt placement (Table 4.4). Again patients did better with LPV than MPV shunts, the greater differences occurring in mRS grades according to intention to treat analysis ($p=0.06$).

Complications of shunt placement

Subdural effusions were the most frequent complication. They were found in 53% of our patients (Table 4.5) and were bilateral in 80% of those cases. Subdural effusions were already visible on the first follow-up CT scan in 84% of patients and resolved spontaneously in 39% of cases. Of the 61% of SDEs that persisted until the last follow-up examination, the volume decreased in 50%. The majority of SDEs were hypodense; some contained hyperdense portions and only a few were fully hyperdense. The diffe-

rence between the two groups was striking because SDEs were present in 71% of patients with LPV shunts and in 34% of patients with MPV shunts ($p=0.0002$).

The influence of subdural effusions on outcome was limited for both the LPV and MPV shunt groups (Table 4.6). Clinically most SDEs seemed to be asymptomatic. Surgical evacuation was necessary in eight cases, four from each treatment group.

All cases of extraperitoneal or ventricular displacement, disconnection of the shunt and infection required surgical treatment.

Table 4.3. Primary and secondary outcome measures related to shunt type in 96 patients with NPH according to intention-to-treat and efficacy analyses*

Outcome measure	LPV group (49 patients)	MPV group (47 patients)	p value
<i>Intention-to-treat analysis</i>			
last NPH scale score	25.8 ± 31.7	15.5 ± 34.3	0.13
mean NPH scale score	25.2 ± 23.4	21.0 ± 25.6	0.40
last mRS grade	1.27 ± 1.41	0.68 ± 1.58	0.06
mean mRS grade	1.09 ± 1.14	0.74 ± 1.22	0.15
last gait scale score	31.8 ± 46.6	22.1 ± 49.0	0.32
last dementia scale score	18.7 ± 23.5	6.1 ± 31.3	0.03
<i>Efficacy analysis</i>			
last NPH scale score	31.3 ± 23.4	30.1 ± 19.6	0.78
mean NPH scale score	26.4 ± 22.0	28.7 ± 19.2	0.59
last mRS grade	1.34 ± 1.28	1.06 ± 1.17	0.26
mean mRS grade	1.11 ± 1.11	0.98 ± 1.01	0.53
last gait scale score	41.1 ± 29.9	41.4 ± 27.9	0.97
last dementia scale score	21.2 ± 21.4	16.6 ± 19/5	0.28

* Values given for each group are expressed as the mean ± standard deviation. Probability values were determined by using Student's t-test.

Ventricular width

Measurement of cerebrospinal fluid (CSF) spaces on CT scans yielded a significantly greater reduction in ventricular size after shunt placement in patients with an LPV shunt than in those with an MPV shunt ($p=0.009$) and also in patients with SDEs compared with those without SDEs ($p<0.001$).

Table 4.4. Level of improvement related to shunt type in 96 patients with NPH according to intention-to-treat and efficacy analyses

Level of improvement	NPH scale		mRS grade	
	LPV group N = 49	MPV group N = 47	LPV group N = 49	MPV group N = 47
<i>Intention-to-treat analysis (%)</i>				
None	33	41	26	47
Moderate	14	21	29	25
Marked	20	17	29	15
Excellent	33	21	16	13
<i>Efficacy analysis (%)</i>				
None	25	26	24	36
Moderate	20	23	31	34
Marked	22	23	29	17
Excellent	33	28	16	13

DISCUSSION

The Dutch Normal-Pressure Hydrocephalus Study is the first trial in which LPV and MPV shunts have been compared according to a prospective and randomized design. Intention-to-treat analysis yielded a strong tendency toward better results for patients with an LPV shunt compared with those with an MPV shunt, achieving statistical significance only with the dementia scale and almost achieving it with the mRS. The only corroborating evidence for these results comes from the retrospective study conducted by McQuarrie and colleagues.⁶⁰ For NPH patients with early disease low-pressure shunts resulted significantly more often in improvement in gait and reduction in ventricular size.

Shunt characteristics

The Medos Hakim shunt was selected because its actual working pressure corresponds best to the manufacturer's specifications and remains constant over time.¹²¹ Trost, et al.,¹²¹ tested different types of shunts in vitro and concluded that the Medos Hakim spring-ball valve had an excellent pressure-flow relationship and a stable prolonged reliability. For other shunt types they found deviations of up to 800%. We measured the working pressure of the valve just before implantation. Deviations from

the manufacturer's specifications were relatively small for both shunt types and the range of working pressures did not overlap.

Table 4.5. Shunt-related complications in 96 patients with NPH

Type of complication	Total no. of cases N = 96	LPV group N = 49	MPV group N = 47
Subdural effusions	51	35	16
Transient	20	11	9
Persistent	31	24	7
Requiring surgical therapy	8	4	4
Ventricular displacement	9	6	3
Extraperitoneal localization	7	5	2
Infection	3	0	3
Disconnection	3	2	1
Transient paresis N. VI	3	2	1
Epileptic seizures	1	0	1
Intracerebral hematoma	2	1	1
Total	79	51	28

Subdural effusions

Subdural effusions have been observed in up to 28% of patients with NPH who have shunts.^{10;11;18;42;49;69;81;90;100;122} If cases of transient effusions are excluded, 32% of our patients exhibited SDE. This high incidence can be attributed partly to the many follow-up CT scans and the very strict CT criteria. Other reasons are the low resistance of the Medos Hakim system, leading to a greater CSF flow and, of course, the insertion of LPV shunts in one-half of the patients. The LPV shunts were indeed accompanied by a significantly higher percentage of SDEs.

Subdural effusions have to be characterized as a severe complication for the eight patients who required surgical evacuation. However, overall outcome did not seem to be affected by SDE because no differences could be detected between patients with and without SDE. An interesting finding of this study is that outcome was better for patients with an LPV shunt despite the many SDEs. The LPV shunt group

also displayed a significantly larger reduction in ventricular volume because of the valve as well as the SDEs.

Table 4.6. Influence of subdural effusions (SDE) on primary outcome measures according to efficacy analysis in patients with NPH who had low or medium-high pressure shunts*

		Outcome measure	
Group	No. of cases	Last NPH scale score	Last mRS grade
<i>LPV group</i>			
Without SDE	14	34.0 ± 22.0	1.50 ± 1.45
With SDE	35	30.2 ± 24.2	1.29 ± 1.23
p value		0.61	0.60
<i>MPV group</i>			
Without SDE	31	28.9 ± 19.6	1.16 ± 1.10
With SDE	16	32.3 ± 20.1	0.88 ± 1.31
p value		0.58	0.43
<i>All patients</i>			
Without SDE	45	30.5 ± 20.3	1.27 ± 1.21
With SDE	51	30.9 ± 22.8	1.16 ± 1.21
p value		0.94	0.67

* Outcome measures are expressed as the mean ± standard deviation. Probability values were determined by using Student's t-test.

How does a shunt work?

The common opinion is that shunts remove the excess of CSF, resulting in a decrease in CSF pressure. Unfolding of the brain is then thought to take place only when ventricular pressure is lower than intraparenchymal venous pressure.¹² The larger the ventricles, the greater the pressure gradient required for reversal of hydrocephalus.⁴⁷ Pang and Altschuller⁸⁷ described 12 patients with very large ventricles and low CSF pressure whose symptoms and signs of shunt malfunction had to be treated by external ventricular drainage at subzero pressure. In a series of 60 patients with NPH, those with a baseline pressure below 140 mmH₂O before shunt placement benefited little from medium-pressure shunts.⁷⁶ Magnaes⁷⁶ advocated a shunt working pressure of 50 mmH₂O below CSF pressure. Mean baseline pressure in our study was 150 mmH₂O,

the lowest value being 70 mmH₂O. On the basis of the aforementioned observations, therefore, a low pressure shunt would be the better choice.

Some investigators hold the view that shunts are effective primarily because the Rcsf is lowered. In one study Rcsf and baseline CSF pressure were measured before and after shunt implantation.¹¹² The postoperative baseline pressure was not related to the working pressure of the shunt, but the reduction in baseline pressure correlated well with the reduction in Rcsf. Patients with NPH who received a programmable shunt system improved only during the first 3 months at a high working pressure. In this period baseline pressure remained unchanged, indicating that the improvement was due to a reduction in Rcsf.⁶⁸ If reduction of CSF outflow resistance is considered more important for ventricular reduction medium-pressure shunts with a low resistance might be preferred.

The better outcome and the greater decrease in ventricular size in patients with LPV shunts indicate that shunt function is certainly determined by working pressure and thus by the gradients between intraparenchymal venous pressure, ventricular pressure and shunt working pressure. The contribution of Rcsf reduction is less clear. Studies in which the function of shunts with variable resistance and the same working pressure are compared are not available. The high incidence of SDEs following shunt placement with the low-resistance Medos Hakim valve perhaps demonstrates that shunt resistance is important. An argument against the reduction-of-Rcsf hypothesis is the fact that postoperative normalization of Rcsf in a few of our patients with an MPV shunt did not lead to improvement. Furthermore, prediction of outcome by Rcsf was somewhat disappointing,¹⁴ suggesting that a disturbance of Rcsf is not the only pathogenic factor in NPH and that normalization of Rcsf is not the most important shunt function.

Treatment of overdrainage

We advocate the use of low pressure shunts for NPH, but how does one prevent overdrainage? One solution is the use of an antisiphon device that reduces CSF flow when the patient is in the upright position. However, this reduction of CSF flow carries the risk of underdrainage⁹⁸ and siphoning alone does not explain the large difference in the development of SDEs between LPV and MPV shunts. The working pressures of the two differ by only 60 mmH₂O, which pales into insignificance besides the hydrostatic pressure of the long distal catheter.

Variable resistance or flow-regulated valves, like the Orbis-Sigma Valve (Cordis Corp., Miami, FL), might be an answer; however, subdural hematomas and slit ventricles also occur after insertion of this shunt.^{120;132} The advantages of a programmable valve such as the Medos Hakim with 18 pressure settings are that shunt pressure

can be better adjusted to CSF dynamics and the valve can be reprogrammed after implantation to prevent or treat overdrainage.¹²

Conclusions

Outcome in our 96 patients who had NPH was better for those who received the LPV rather than the MPV nonprogrammable Medos Hakim shunt, although the differences did not reach statistical significance for most of the outcome measures. The incidence of SDEs was high, but their influence on outcome was limited. The high rate of complications of shunt placement is an additional indication of the need to proceed with caution in this vulnerable NPH population. Based on the results of this study, treatment of NPH with a low-pressure shunt is recommended.

5

THE ROLE OF CEREBROVASCULAR DISEASE

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ABSTRACT

Object. To determine the prevalence of cerebrovascular disease (CVD) and four risk factors for CVD among patients with normal pressure hydrocephalus (NPH) and to assess their influence on the outcome of shunting.

Methods. A cohort of 101 NPH patients was shunted and followed for one year. Gait disturbance and dementia were quantified by an NPH-scale and handicap by a modified Rankin scale (mRS). Primary outcome measures were differences between preoperative and last NPH scale and mRS scores. The occurrence of the risk factors hypertension, diabetes mellitus, ischemic heart disease and peripheral vascular disease was recorded. CVD was defined as a history of stroke or a computed tomographic (CT) scan showing infarcts or moderate to severe white matter hypodense lesions (WMHLs).

Results. The prevalence of risk factors for CVD was higher for the 45 patients with CVD than the 56 without CVD. Risk factors did not influence outcome after shunting. Intention-to-treat analysis revealed that the mean improvement in the various scales was significantly worse for patients with a history of stroke ($n=14$) or CT-scans exhibiting infarcts ($n=13$) or WMHLs ($n=32$) than for those without CVD. The proportion of shunt responders was also significantly lower among patients with than those without CVD ($p=0.02$).

Conclusions. We identified a subgroup of NPH patients with CVD that showed disappointing results of shunting. CVD was an important predictor of poor outcome.

INTRODUCTION

The pathogenesis of normal-pressure hydrocephalus (NPH) is thought to be disturbed absorption of cerebrospinal fluid (CSF) caused by an increase in the resistance to outflow of CSF (Rcsf), resulting in an increase in CSF pressure and ventricular dilatation. This mechanism is not disputed for symptomatic NPH but largely unexplained for idiopathic NPH. According to the sparse neuropathological studies of idiopathic NPH leptomeningeal fibrosis was often absent or it was not clear whether this fibrosis was severe enough to impair absorption of CSF.^{2,8;28;45;61;93;107} The lack of correlation between Rcsf, baseline CSF pressure and ventricular size also suggests that increased Rcsf is not the only etiologic factor.^{14;16;58;116}

Several authors have drawn attention to the association between cerebrovascular disease (CVD) and idiopathic NPH. Risk factors for CVD were found significantly more often among patients with NPH than controls.^{23;40;63} Computed tomographic (CT) evidence of CVD, such as white matter hypodense lesions (WMHLs), was also more common among NPH patients.^{20;65} Two studies provide evidence that the association of CVD and NPH is indicative of an unfavorable prognosis for the result of shunting.^{62;69}

In the Dutch NPH Study 101 patients with mainly idiopathic NPH received a ventriculoperitoneal shunt and were followed for one year. The objectives of the present study were to determine the relative frequencies for CVD and four risk factors for CVD in this group of NPH patients and to assess their influence on the outcome of shunting. A secondary aim was to examine whether our data support a causal relationship between CVD and NPH.

PATIENTS AND METHODS

Measurement of gait disturbance and dementia

Gait disturbance was quantified by a gait scale, that evaluates the presence of 10 features of gait and measures the number of steps and seconds required for a 10-metre walk.¹⁶ Dementia was assessed by a dementia scale comprising the 10-word test, digit span forwards and backwards, trail making and finger tapping.¹⁶ 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),¹²⁷ used to obtain a disability score, was extended to a 7-point scale by inserting mRS grade 4 (defined as moderate disability, partially independent, needing assistance for less than 50% of the day).

Eligibility

Between September 1990 and July 1995 101 NPH patients (89 idiopathic and 12 chronic symptomatic) were enrolled fulfilling the following inclusion criteria:

- 1) a gradually developed gait disturbance of both legs, 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 disability mRS score of at least 2;
- 4) a CT-scan showing a communicating hydrocephalus with an Evans' index of at least 0.3 and a ventricular index greater than 0.8,¹⁶ without clinically relevant parenchymal lesions, the sum of the 4 largest convexity sulci being less than 25 mm (real size).

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

Study design

All patients underwent a lumbar constant-flow infusion test⁵⁶ and received a Medos Hakim spring ball valve shunt, irrespective of the Rcsf value. They were randomized for a low or a medium-high working pressure.¹⁵ The gait scale, dementia scale and mRS were determined prior to and 1, 3, 6, 9 and 12 months after surgery. CT-scans were obtained preoperatively and after 1, 6 and 12 months.

Evaluation of cerebrovascular disease and its risk factors

Six risk factors for CVD were recorded, using the following definitions: 1) arterial hypertension, a documented history of hypertension (blood pressure exceeding 160/90 mmHg) or the use of antihypertensive drugs; 2) diabetes mellitus, the use of antidiabetic drugs; 3) cardiac disease : ischemic heart disease, a history of myocardial infarction or angina pectoris, or ischemic electrocardiographic changes; documented atrial fibrillation or congestive heart failure; 4) peripheral vascular disease, a documented history of intermittent claudication or vascular surgery; 5) male gender; 6) advancing age older than the median age (74 years). The criterion for CVD was the presence of at least one of the following: 1) a documented history of ischemic or hemorrhagic stroke; 2) infarct(s) on the CT-scan at entry; 3) moderate or severe WMHs on the CT-scan at entry defined as a total ischemic score (TIS) of at least 2.¹²⁵

Outcome measures

Primary outcome measures were the differences between the preoperative and the last NPH scale and mRS scores. Because it proved easier to improve starting at a high than

at a low level of the NPH scale, these changes were expressed as a percentage of the preoperative value.¹⁴ The more even distribution of handicaps over the grades of mRS justified the use of numerical differences. Secondary outcome measures used for this study were the differences between the preoperative and last gait scale and dementia scale scores. Improvement was classified using the primary outcome measures (Table 5.1).

Table 5.1. Classification of improvement in the Dutch Normal-Pressure Hydrocephalus study

Level of improvement	Improvement in NPH scale score (%)	Improvement in the modified Rankin scale (grades)
None	< 15	< 1
Moderate	15-29	1
Marked	30-44	2
Excellent	≥ 45	≥ 3

* NPH scale = gait scale + dementia scale

Follow-up

Five of the 101 patients died of diseases unrelated to the shunt before the first follow-up at one month. Causes were stroke, cardiac failure, mesenteric arterial thrombosis, pneumonia and head injury. Therefore, the effect of CVD on outcome could be investigated for 96 patients. Eleven patients died during follow-up due to pneumonia (three patients), cardiac failure (two patients), stroke (two patients), peritonitis (one patient) and unknown causes (three patients). One patient was lost after 3 months because he returned to his native country, leaving 84 patients with a complete follow-up of 12 months. The mean follow-up period was 10.9 ± 3.0 months. WMHLs were also assessed on the last follow-up CT-scan. The occurrence of stroke during the one-year follow-up period was recorded as well.

Statistical analysis

The results of shunting were studied by comparing the means of the primary and secondary outcome measures found for patients with and without CVD with Student's t-test. The proportions of patients exhibiting improvement in each group were compared by the

chi-square test. Intention-to-treat analysis was performed using all outcome information available at 12 months or the last follow-up. Multiple regression analysis was performed to assess multivariately the simultaneous influence of the three components of CVD on the outcome measures.

RESULTS

Prevalence of cerebrovascular disease and its risk factors

Fifty-three patients presented with at least one vascular risk factor, age and gender excluded (Table 5.2). Cardiac diseases were present in 21 patients, of whom all had ischemic heart disease, three had atrial fibrillation and 1 patient had a history of

Table 5.2. Prevalence of risk factors for cerebrovascular disease in 101 NPH patients

	All patients N=101		Patients with cerebrovascular disease N=45		Patients without cerebrovascular disease N=56	
	No of cases	%	No of cases	%	No of cases	%
Hypertension	28	28	16	36	12	21
Diabetes Mellitus	15	15	6	13	9	16
Cardiac Disease	21	21	11	24	10	18
Peripheral vascular disease	4	4	3	3	1	2
Male gender	60	59	24	24	36	64
Age \geq 74	52	51	27	60	25	45

congestive heart failure. Hypertension, cardiac disease and peripheral vascular disease occurred more frequently among patients with CVD, but diabetes mellitus was evenly distributed between patients with and without CVD. The highest percentages of hypertension and cardiac disease were found for patients with a history of stroke or infarcts on CT. Patients with CVD were older and more often female.

In total 45 of the 101 patients presented with one or more signs of CVD (Table 5.3). Because conditions that can affect gait were an exclusion criterion, patients who had suffered ischemic events before entry into the study did not show a residual deficit. The infarcts on CT, mostly of the lacunar type, were clinically silent since symptomatic parenchymal lesions were an exclusion criterion as well.

The presence of risk factors for CVD did not show a correlation with the initial clinical picture. Patients with CVD tended to have smaller ventricles and a somewhat more severe NPH syndrome at entry, as quantified by the NPH scale and mRS scores (Table 5.4). Their Rcsf was significantly lower.

Using the total ischemic score, the WMHLs on the last CT-scan increased in 9%, decreased in 9% and did not change in 82% of the cases. Fifteen patients developed an ischemic stroke during follow-up.

Table 5.3. Prevalence of cerebrovascular disease in 101 NPH patients

	No of cases
Cerebrovascular disease	45
History of stroke	14
White matter hypodense lesions	
absent or slight (TIS* 0,1)	69
moderate or severe (TIS* 2-4)	32
Infarctions on CT	13
No cerebrovascular disease	56

* TIS = total ischemic score

Cerebrovascular disease related to outcome after shunting

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

According to intention-to-treat analysis patients with a history of stroke and those with WMHLs or infarcts on their CT scan showed significantly less improvement (Table 5.5). The largest differences in outcome were found between the 43 patients classified as having CVD on at least one account and the 53 patients without CVD. Multiple regression analysis revealed that, out of the three components of CVD, WMHLs and infarcts on CT 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 CVD. A history of stroke did not contribute any further.

Another way of analyzing outcome is to calculate the proportion of shunt responders, defined here as any improvement in the NPH scale (Table 5.1). Of the 43 patients exhibiting CVD 21 (49%) were categorized as improved and 22 (51%) as unimproved, whereas 39 (74%) of the 53 patients without CVD responded to shunting and 14 (26%)

did not. The difference between the two groups was significant ($p=0.02$). This difference could not be attributed to the type of shunt used. The low and medium-high pressure shunts were equally distributed among the patient groups with and without CVD and the results of shunting for the 2 valve types within both groups were not significantly different.

Table 5.4. Baseline variables related to cerebrovascular disease in NPH patients

Characteristic	Patients with cerebrovascular disease N=45		Patients without cerebrovascular disease N=56		p-value
	Mean	SD	Mean	SD	
Ventricular width	1.16	.15	1.21	.16	.14
CSF outflow resistance	15.9	4.3	18.9	7.1	.02
modified Rankin scale	3.9	1.0	3.5	1.4	.20
NPH scale*	51.4	13.1	46.0	17.1	.08

*NPH scale = gait scale + dementia scale

DISCUSSION

Prevalence of cerebrovascular disease and its risk factors

Risk factors for CVD among patients suffering from idiopathic NPH have been studied before. Arterial hypertension was present in 74% of the 19 patients reported by Graff-Radford et al.⁴⁰ and 83% of the 65 patients of Krauss et al.⁶³ compared to 31% of Larsson's 74 patients⁶⁹ and 28% in the present study. These considerable differences cannot be attributed to the prevalence of hypertension in controls of the same age, which was around 35% in studies from Germany and Italy^{23,63} and 30% in one from the Netherlands.⁸² Part of the discrepancy can be explained by differences in definition. Excluding blood pressure measurements taken during the study, like we did, Krauss et al. still found hypertension in 60% of their patients.⁶³ They also found diabetes mellitus in 49% and ischemic heart disease in 57% of the NPH patients, percentages exceeding those reported in large stroke studies.^{4,124} The relative frequencies of patients with a history of stroke⁶³ and lacunar infarcts on CT⁴⁰ were also higher than in our study. The NPH populations investigated by Graff-Radford and Krauss were obviously different from Larsson's and that of the present study.

Although our study of risk factors for CVD was not complete, with smoking history and the cholesterol level missing, it is unlikely that these two would have altered the

finding that vascular risk factors were not related to outcome after shunt placement. Such a relationship is not obvious since we are dealing with risk factors for CVD that in turn can be considered a risk factor for the surgical treatment of NPH patients.

Table 5.5. Influence of different expressions of cerebrovascular disease* on outcome of shunting in 96 evaluable NPH patients

IMPROVEMENT according to intention-to-treat analysis									
	NPH SCALE [#]			GAIT SCALE		DEMENTIA SCALE		RANKIN SCALE	
	N	Mean (%)	SD	Mean (%)	SD	Mean (%)	SD	Mean (%)	SD
<i>History of stroke</i>									
Yes	13	2.2	35.5	6.0	47.7	-0.3	37.8	0.15	1.77
No	83	23.7	2.1	30.3	47.2	14.6	26.0	1.11	1.44
p-value		0.03		0.09		0.08		0.03	
<i>WMHLs*</i>									
moderate or severe	30	10.2	31.2	12.6	45.1	4.7	27.7	0.40	1.30
absent or slight	66	25.6	33.3	33.6	47.8	16.1	27.8	1.24	1.54
p-value		0.04		0.05		0.06		0.01	
<i>Infarcts on CT</i>									
Yes	12	-5.3	47.4	-14.7	73.6	4.0	28.5	0.25	2.22
No	84	24.5	29.3	33.0	40.1	13.8	28.0	1.08	1.37
p-value		0.003		0.001		0.26		0.07	
<i>Cerebrovascular disease*</i>									
Yes	43	8.3	36.2	8.7	54.7	5.0	31.0	0.51	1.50
No	53	30.8	27.1	41.9	35.3	18.7	24.1	1.35	1.42
p-value		0.001		0.001		0.02		0.0006	

* Cerebrovascular disease : at least one of the following: history of stroke, moderate or severe white matter hypodense lesions or infarcts on CT; * WMHLs = white matter hypodense lesions; # NPH scale = gait scale + dementia scale

The causes of WMHLs are not fully understood partly because the neurological and histological abnormalities are nonspecific.⁸⁹ WMHLs are closely associated with stroke and arterial hypertension.^{6,21,22,51,72} Furthermore, the risk for future stroke is increased for patients exhibiting WMHLs.^{50,88,126} To a lesser extent WMHLs are associated with Alzheimer's disease,^{37,51} but we took particular care to exclude that condition. Patients

suffering from an acute or subacute disturbance of CSF circulation may develop periventricular lucencies due to transependymal CSF leakage. In the present study the NPH was chronic in nature; moreover the WMHLs lacked the typical periventricular caps and did not change after shunting in the majority of cases. Therefore, we consider WMHLs as an expression of white matter ischemia.

Although magnetic resonance imaging (MRI) is more sensitive for detection of WMHLs, CT is more specific for prediction of symptomatic CVD.⁷³ The occurrence of WMHLs on MRI has been addressed in two studies. WMHLs were detected in a significantly higher proportion of patients with NPH than controls.^{20,65} The prevalence of WMHLs in NPH patients (93%²⁰ and 70%⁶⁵) was of course higher than in our CT study (56%).

Cerebrovascular disease related to outcome of shunting

The extension of WMHLs on MRI, quantified by a 24 point scale, was inversely related to the degree of clinical improvement after shunting with correlation coefficients in the 0.3 range.⁶⁴ Using a different type of analysis we were able to confirm that more extensive WMHLs on CT are associated with less favorable results of shunting. Since 4 out of 7 patients with the most severe WMHLs responded to shunting, we agree with Krauss et al. that these patients should not automatically be denied shunting.⁶² In contrast to their findings we could not demonstrate a relationship between WMHLs and preoperative NPH and modified Rankin scale scores.

Both a history of stroke and computed tomographic infarcts were predictors of an unfavorable outcome. The greatest difference in mean improvement was found between patients with at least one expression of CVD and patients without CVD. In a study of 74 carefully evaluated NPH patients the least improvement was also obtained for a subgroup with NPH secondary to CVD.⁶⁹ The high percentage of our patients suffering from stroke during the one-year follow-up period further underlines the importance of CVD in idiopathic NPH and could be a reason to refrain from shunting in doubtful cases.

Pathogenic role of cerebrovascular disease

The question is whether CVD may actually cause NPH. The neuropathological evidence is meager. Examination of 25 brain biopsies of patients suspected of NPH revealed meningeal fibrosis in only 12 and signs of Alzheimer's disease and CVD in 10 cases, suggesting that NPH may be a parenchymal disease in a number of patients.⁸ Autopsy showed hypertensive cerebrovascular disease with normal leptomeninges and arachnoid villi in some patients with the typical clinical and radiological features of NPH.^{28,45,61} The postmortem findings on 7 NPH patients consisted of both Binswanger's encephalopathy and focal leptomeningeal fibrosis as well as reduction of arachnoidal granulations.²

An answer to the above question is thwarted by the difficult clinical diagnosis of NPH,¹⁶ in particular the distinction from Binswanger's disease. According to Galassi both diseases constitute a continuous spectrum that will narrow in the course of time.³⁶ Patients with long-standing NPH will develop periventricular ischemia and ventricular size will increase in Binswanger's disease.

A review of the literature on CSF dynamics in NPH shows that most investigators agree that increased Rcsf is the primary pathogenic factor. A few, however, hold the view that changes in compliance are the initial cause of ventricular dilatation.^{102;104} In animals hydrocephalus could be induced by increasing the intraventricular pulse pressure,⁹¹ increasing pulse pressures were recorded before there was an increase in intracranial pressure in patients who developed hydrocephalus after subarachnoid hemorrhage.¹⁰¹ These observations provide some support for the notion that arterial hypertension might cause NPH by increasing the intraventricular pulse pressure,⁴⁰ especially because a widened pulse pressure is more common in case of hypertension in the elderly.⁹⁶

WMHLs and deep white matter infarctions supposedly are more important for the development of NPH.^{20;28} The vascular lesions will result in a reduction of 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. Secondly, the arachnoid space at the convexity may be compressed, producing an increase in Rcsf.

What evidence from this study supports an etiologic role of CVD in idiopathic NPH? We could not find a relationship between Rcsf, ventricular size, reduction of ventricular size after shunting, severity of the NPH syndrome at entry and degree of improvement after shunting,^{14;16} suggesting that NPH is not an entity but a syndrome with different underlying causes. Secondly, NPH patients with CVD had a lower Rcsf, possibly indicating parenchymal involvement rather than a CSF circulation disorder. Furthermore, patients with moderate or severe WMHLs exhibited slightly irregular ventricular walls explainable by retraction of periventricular tissue.

On the other hand, one might argue that CVD is a coincidental disease in a subgroup of NPH patients. Some of the WMHLs and infarcts were located in the deep white matter and not periventricular, as presumed by the "compliance" hypothesis. The findings of a previous study were not in agreement with this hypothesis either.¹¹⁷ We demonstrated in a large group of hydrocephalic patients that compliance was not an independent parameter but was chiefly determined by Rcsf. Finally, the periventricular parenchymal changes that reduce compliance seem largely irreversible, which is less compatible with improvement after shunting.

We conclude that the prevalence of CVD in patients with NPH is high. CVD is an important predictor of an unfavorable outcome of shunting although not to such a degree that this operation should be discouraged beforehand. The difficult question of a causal relationship between CVD and NPH is not settled. A study with a larger number of NPH patients specifically designed to evaluate CVD is required.

6

HOW TO SELECT PATIENTS FOR SHUNTING? AN ANALYSIS OF FOUR DIAGNOSTIC CRITERIA

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Submitted

ABSTRACT

Object. Comparison of the predictive value of four "diagnostic tests" for the outcome of shunting in patients with normal-pressure hydrocephalus (NPH).

Methods. A group of 95 NPH patients who received a shunt was followed for one year. Gait disturbance and dementia were quantified by an NPH scale and handicap by a modified Rankin scale (mRS). Primary outcome measures were differences between the preoperative and last scores of both the NPH scale and the mR scale. Clinical and computed tomographic (CT) findings typical for NPH, absence of cerebrovascular disease (CVD) and a resistance to outflow of cerebrospinal fluid (Rcsf) ≥ 18 mm Hg/ml/minute were designated as a positive test outcome and clinical and CT findings compatible with NPH, presence of CVD and an Rcsf < 18 mmHg/ml/minute as a negative test outcome.

Results. For each of the four tests the proportion of patients classified as improved and the degree of improvement were significantly greater for those with positive than with negative test results. Rcsf measurement was the only significant prognostic factor for the improvement ratio in NPH scale and CT in mR scale according to multivariate logistic regression analysis. CT and CVD were the most important predictors of the degree of improvement in NPH as well as mR scale with multiple regression analysis. The accurate predictive value of the combination of typical clinical and CT findings was 0.65, that of the positive test results of Rcsf, clinical and CT findings 0.74.

Conclusion. The best strategy is to shunt NPH patients if their Rcsf is ≥ 18 mmHg/ml/minute or, when the Rcsf is lower, if their clinical as well as their CT findings are typical for NPH.

INTRODUCTION

The primary objective of the Dutch Normal Pressure Hydrocephalus Study was to determine the predictive value of the resistance to outflow of cerebrospinal fluid (Rcsf) for the outcome of shunting in patients with normal-pressure hydrocephalus (NPH). We found that an Rcsf of at least 18mmHg/ml/min reliably predicts a good outcome.¹⁴ We also reported that the results of shunting were significantly worse for patients with coexistent cerebrovascular disease (CVD).¹⁷ Many authors, however, have stressed the importance of the clinical picture and to a lesser extent that of computed tomographic (CT) findings for the selection of NPH patients for shunting.^{10;13;19;39;42;43;52;53;90;113;134} The purpose of the present study was to examine the prognostic value of clinical and CT findings for predicting the outcome after shunting and to compare them with those of CVD and Rcsf. The prognostic values will be studied for each parameter separately (univariate analysis) as well as for combinations of parameters (multivariate analysis).

PATIENTS AND METHODS

Measurement of gait disturbance and dementia

Gait disturbance was quantified by a gait scale that evaluates the presence of 10 features of gait and measures the number of steps and seconds required for a 10-metre walk, range 2-40. Dementia was assessed by means of a dementia scale comprising the 10-word test, digit span forwards and backwards, trail making and finger tapping, range 4-40. Both scales are described in detail elsewhere.¹⁶ To create one neurological outcome measure the scores for gait and dementia were added, yielding the NPH scale, range 6-80. The modified Rankin (mR) scale,¹²⁷ used to obtain a handicap score, was extended to a 7-point scale by inserting mR scale grade 4 (defined as moderate disability, partially independent, needing assistance for less than 50% of the day).

Eligibility

Between September 1990 and July 1995 101 NPH patients, who fulfilled all of the following inclusion criteria, were enrolled:

- 1) a gradually developed gait disturbance of both legs, unexplained by other conditions, and a gait scale score of at least 12;
- 2) 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 mR scale score of at least 2;
- 4) a CT scan showing communicating hydrocephalus with an Evans' index of at least 0.3 and a ventricular index > 0.8 ,¹⁶ without clinically relevant parenchymal lesions, the sum of the 4 largest sulci at the convexity being < 25 mm (real size).

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

Study design

All patients underwent a lumbar constant flow infusion test^{14;56} and received a Medos Hakim spring ball valve shunt, irrespective of the Rcsf value. They were randomized to have a low or medium-high working pressure.¹⁵ The gait scale, dementia scale and mR scale were determined prior to and 1, 3, 6, 9 and 12 months after surgery. CT scans were obtained preoperatively and after 1, 6 and 12 months.

The history and clinical signs, including the neurological examination on admission as well as all preoperative CT-scans, were assessed independently by two of the authors (A.J.W.B, J.T.J.T) after entrance into the study. Both the clinical and CT findings were classified as being typical for or compatible with NPH (Fig. 6.1). In case of disagreement consensus was reached by deliberation. CVD was defined as the presence of at least one of the following: 1) a documented history of stroke; 2) infarct(s) on the CT-scan at entry; 3) moderate or severe white matter hypodense lesions (WMHLs) on the CT-scan at entry defined as a total ischemic score of at least 2.¹²⁵ Clinical and CT findings typical for NPH, absence of CVD and an Rcsf ≥ 18 mmHg/ml/minute were designated as a positive test outcome for the diagnosis of NPH. Clinical and CT findings compatible with NPH, the presence of CVD and an Rcsf of less than 18 mmHg/ml/minute were considered a negative test outcome for the diagnosis of NPH.

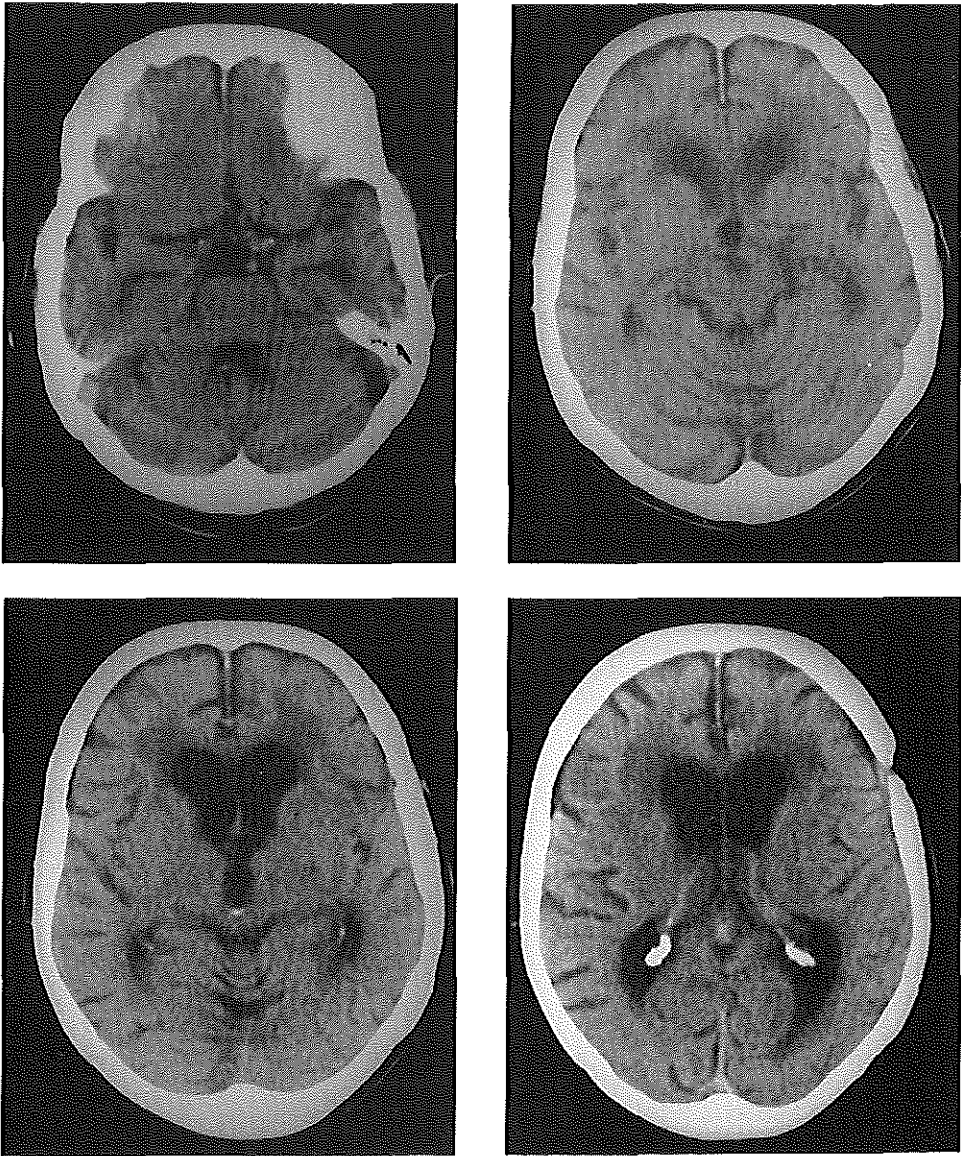
Follow-up

Of the 101 patients, five died of diseases unrelated to the shunt before the first follow-up at one month. Causes were stroke, cardiac failure, mesenteric arterial thrombosis, pneumonia and head injury. Rcsf could not be determined for one patient, probably due to incorrect positioning of the needle, leaving a total of 95 cases with evaluable follow-up. Another 10 patients died during follow-up due to pneumonia (two patients), cardiac failure (two patients), stroke (two patients), peritonitis (1 patient) and unknown cause (three patients). One patient was lost to follow-up after 3 months because of remigration to his native country, leaving 84 patients with a complete follow up of 12 months. Mean follow-up was 10.9 ± 3.0 months.

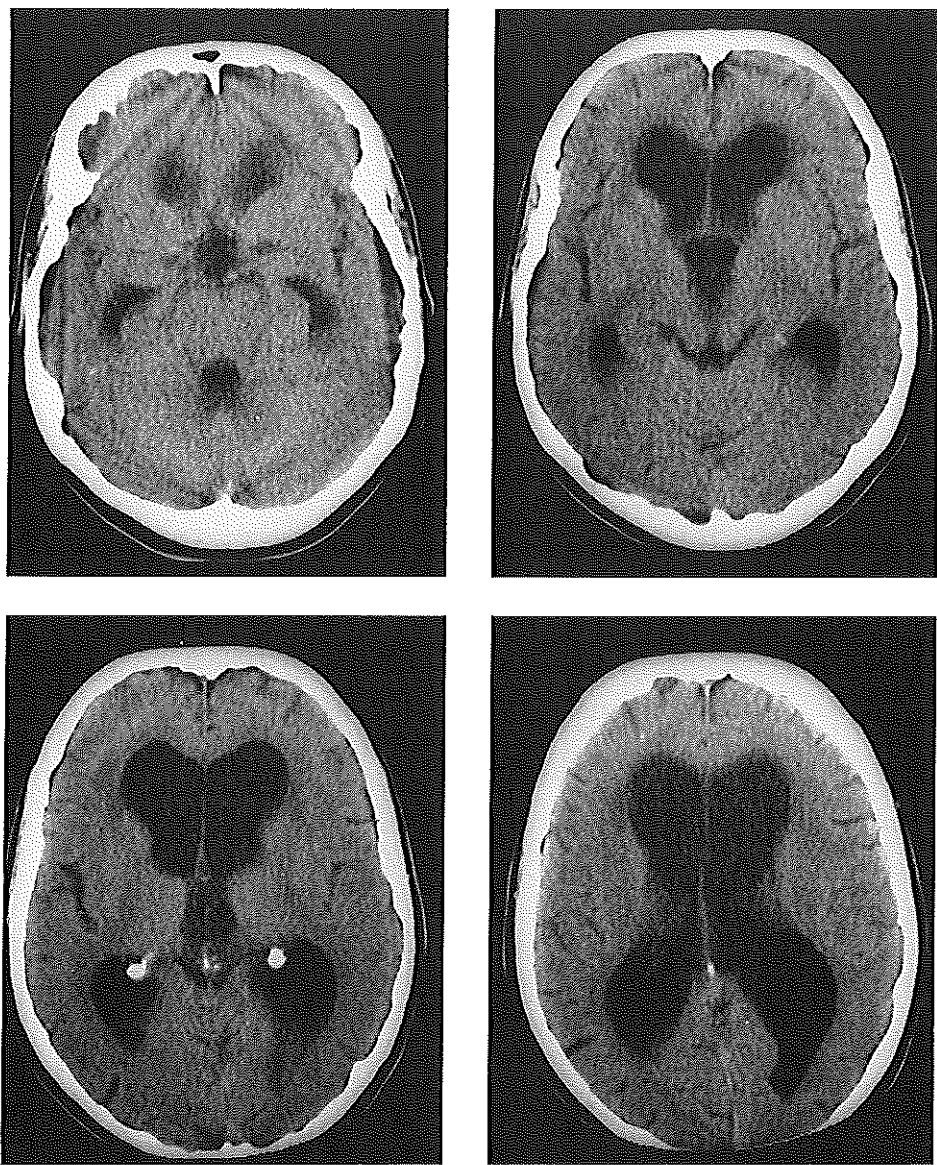
Outcome measures and analysis

The two primary outcome measures for this report were the relative difference in the preoperative and the last NPH scale scores, expressed as percentage of the

Fig. 6.1. Computed tomography compatible with NPH (a) and typical for NPH (b).



a. Computed tomography compatible with NPH of a 84 year old woman, who had developed full blown NPH symptomatology 7 months after evacuation of a subdural hematoma. She could not walk anymore and a moderate dementia and urinary incontinence were present.



b. Computed tomography typical for NPH of a 70 year old female with a history of hypertension and diabetes mellitus. In a year she developed a slowly progressive gait disturbance, a mild cognitive deficit and imperative micturition.

preoperative score, and the absolute difference in the preoperative and last mR scale scores.¹⁶ To assess the results of shunting in the 95 evaluable patients, all known serious events that were unrelated to NPH, but clearly interfered with neurological function, were excluded. The deaths of the aforementioned 10 patients and another 17 events, such as stroke, severe cardiac failure and hip fracture, were recorded. For these patients the scores at the last follow-up examination before this event were used to calculate the outcome measures. We called this efficacy analysis in our previous reports.^{14;15}

The results of shunting were studied univariately by comparing the means of the primary outcome measures between patients with positive and negative test results, using the Student's t-test. Multiple regression analysis was performed to assess multivariately the simultaneous influence of the four diagnostic tests on the outcome measures. Outcome was also dichotomized as improved or not improved. Improvement was defined as a decrease of at least 15% in NPH scale or one grade in mR scale between entry and last score. The improvement ratio among patients with positive and negative tests was compared by means of the chi-square test on two by two tables. Finally, odds ratios for single and multiple positive and negative test outcomes were determined with logistic regression.

RESULTS

A summary of the primary outcome measures for the negative and positive outcome of each test is given in Table 6.1. The proportion of patients classified as improved was significantly greater for those with positive than with negative test results. The degree of improvement was also significantly better for 3 of the 4 diagnostic tests. The highest percentage of shunt responders in the NPH scale was found for patients with an Rcsf measurement ≥ 18 mmHg/ml/minute. Computed tomography yielded the largest difference between positive and negative test outcomes in the Rankin scale both for the proportion of improved patients and for the amount of improvement. The number of patients who improved and the degree of improvement despite a negative test were relatively high for all tests. The combination of typical clinical and CT findings was found for 55 patients, 24 of whom presented with an Rcsf ≥ 18 mmHg/ml/min. Four positive tests were found for only 16 patients.

Multiple regression analysis was performed to quantify the effect of the four diagnostic tests on the degree of improvement for the primary outcome measures (Table 6.2). The equations show that the predictive power of the test outcomes was on the same order of magnitude with a CT scan typical for NPH and the absence of CVD being more important. The degree of improvement in NPH scale varied from 15.6% when the four tests were negative to 41.4% when they were all positive. For the Rankin scale the range was

0.3 to 1.9 grades. However, the random variation around the regression equations remained large. The R-square, a measure of the variability of the outcome explained by the different tests, was low.

Table 6.1. Primary outcome measures related to positive or negative outcome of diagnostic tests for 95 NPH patients.

Diagnostic test	NPH scale			RANKIN scale	
	Improved	Improvement		Improved	Improvement
	N	N = 72	Mean \pm SD	N = 66	Mean \pm SD
		%		%	
*Clinical findings negative	29	59	22.5 \pm 22.2	52	.76 \pm 1.09
positive	66	83	34.7 \pm 20.3	77	1.42 \pm 1.24
p-value		.01	.01	.01	.01
*Computed tomography negative	30	60	21.5 \pm 19.3	40	.53 \pm 1.01
positive	65	83	35.3 \pm 21.2	83	1.54 \pm 1.20
p-value		.02	.003	< .0001	< .0001
*Cerebrovascular disease negative	43	65	24.8 \pm 18.6	58	.86 \pm 1.10
positive	52	85	36.1 \pm 22.3	79	1.52 \pm 1.26
p-value		.03	.01	.03	.009
*CSF outflow resistance negative	59	66	27.9 \pm 22.4	61	1.03 \pm 1.19
positive	36	92	35.8 \pm 19.3	83	1.53 \pm 1.25
p-value		.005	.09	.02	.06

* negative = compatible with NPH; positive = typical for NPH; # negative = present; positive = absent; + negative = < 18 mmHg/ml/minute; positive = \geq 18 mmHg/ml/minute

The results of logistic regression analysis are given in Table 6.3. Rcsf measurement was the only significant prognostic factor with the NPH scale as outcome measure, without additional independent information of one of the other tests in stepwise selection. Computed tomography was the only significant predictor in the mR scale. The

combination of typical clinical as well as CT findings yielded an odds ratio of 3.52 (95% CI: 1.31-9.44) for the NPH scale and 5.11 (95% CI: 1.98-13.2) for the mR scale.

Table 6.2. Effect of four diagnostic tests on mean improvement in primary outcome measures assessed with multiple regression analysis.

	Expected mean improvement	R-square
NPH scale	$4.4R_{csf} + 6.4CF + 7.3CVD + 7.7CT + 15.6$	0.15
Rankin scale	$0.18CF + 0.28R_{csf} + 0.37CVD + 0.75CT + 0.27$	0.19

Abbreviations: CF = clinical findings; CT = computed tomography; CVD = cerebrovascular disease; Rcsf = CSF outflow resistance. For negative test insert 0, for positive test insert 1

If the decision to place a shunt had been based on the presence of typical clinical and CT findings, 65% of patients would have shown improvement. The best strategy, that resulted in an improvement ratio of 74%, was to shunt patients if their Rcsf was at least 18 mmHg/ml/minute and, when Rcsf was below that value, if their clinical and CT findings were typical for NPH.

DISCUSSION

Clinical and computed tomographic findings

Since only patients with a diagnosis of NPH were eligible for our study, the classification of their clinical and CT findings as compatible with or typical for NPH requires explanation. Both the clinical and CT diagnoses of NPH are notoriously difficult. The gait disturbance, for instance, has specific features such as a wide based, apraxic gait with small steps and feet appearing glued to the floor. On the other hand NPH gait resembles in many ways the aspecific senile gait disorder with varying pyramidal, extrapyramidal and cerebellar signs.

In diagnosing NPH we followed the normal routine which means that this cohort of patients reflects every day practice. We also tried to prevent the selection of only promising surgical candidates. Over a quarter of our patients had the 2 highest Rankin grades and there was extensive past and present comorbidity.¹⁶

The presence of the classical triad, gait, cognitive and micturition disturbances, is considered the most important predictor of outcome after shunting by many investigators.^{10;11;27;83;90} Drawbacks of these studies were that the number of patients was small, the components of the triad were not well-defined or outcome data were collected

retrospectively. Therefore reliable figures on sensitivity, specificity and positive and negative predictive values for the presence of the clinical triad are lacking.

We have tried to quantify the NPH syndrome and the outcome of shunting by using a gait and dementia scale as well as the Rankin scale. The scores on these scales reflect the severity of the NPH syndrome but not the degree of certainty that the diagnosis is correct. Our classification as compatible with or typical for NPH was based on the overall clinical impression, also taking into account disturbed micturition. Both the univariate and multivariate analyses indicated that the clinical findings were helpful, but they certainly were not the most important prognostic factor.

Table 6.3. Improvement (yes/no) related to diagnostic tests assessed with logistic regression analysis.

Positive diagnostic test	NPH scale			Rankin scale	
	N	OR*	95% CI*	OR*	95% CI*
Clinical findings*	66	2.25	0.68-7.41	1.21	0.38-3.91
Computed tomography*	65	1.59	0.47-5.44	5.65	1.79-17.9
Cerebrovascular disease [#]	52	1.86	0.62-5.56	1.48	0.52-4.17
CSF outflow resistance ⁺	36	4.39	1.25-16.7	2.53	0.83-7.78

* positive = typical for NPH; [#] positive = absent; ⁺ positive = ≥ 18 mmHg/ml/min.

* OR = odds ratio; * CI = confidence interval

With respect to computed tomography, most authors examined single CT parameters and reported that improvement after shunting was associated with absence of cortical atrophy,^{10;11;18;43} presence of periventricular lucencies,¹⁹ enlarged temporal horns,^{71;113} dilatation of the fourth ventricle³⁵ or a widened third ventricle.^{80;134} Methodological problems of these studies were the difficulty of quantification of cortical atrophy, particularly with the older generation CT scanners, the differentiation of periventricular liquorhoea from white matter hypodense lesions and again the number of patients and the quality of the outcome data. In this study the relevant CSF spaces on CT-scans were measured as well but there was too much overlap between shunt responders and non-responders for single measurements to be helpful in predicting outcome. The CT scans were judged to be compatible with or typical for NPH on the basis of the overall interpretation, without knowledge of the

results of the various measurements. Computed tomography proved to be the most powerful predictor of outcome in mR scale according to univariate as well as multivariate analysis.

Vanneste et al¹³⁰ were the first to report on the predictive accuracy of combined clinical and CT data, collected retrospectively from patients shunted between 1980 and 1989. The clinical and CT findings yielded an accurate predictive rate of 75% in their probable NPH group and 65% in our typical group. Comparison of these percentages is difficult because their probable group was smaller (27% versus 58% of the total study population) and contained more symptomatic cases than ours.

Low and medium-high pressure shunts

The second objective of the Dutch Normal-Pressure Hydrocephalus Study was a randomized comparison of low and medium-high pressure non-programmable Medos Hakim shunts. Outcome was better for patients receiving a low than a medium-high pressure shunt, although the differences did not reach statistical significance.¹⁵ Shunt type was not included in the multivariate analysis because it does not play a role in the decision to place a shunt.

Selection for shunting

The NPH syndrome covers a wide spectrum of neurological signs varying from mild gait and cognitive disturbances to akinetic mutism and from the classical triad to an atypical syndrome resembling other conditions of the elderly associated with abnormalities of gait, cognition and micturition. Idiopathic NPH is also a rare condition. Not many neurologists or neurosurgeons will acquire enough expertise to arrive at this difficult diagnosis with confidence. Having seen a great number of NPH patients over the years, we still prefer to have corroborating evidence from additional tests before selecting patients for an operation with often disappointing results and a high complication rate. Only a truly pathognomonic form of the NPH triad, present in less than 25% of cases, is enough to advise surgery without ancillary investigations.

We recommend measurement of Rcsf for the remaining 75% of patients with idiopathic NPH. Lumbar constant flow infusion is preferred since it involves only one lumbar puncture, simple equipment and one hour of time. Rcsf measurement might not be the ideal predictor of outcome, but at least it provides a reproducible number¹¹⁵ that leaves little room for differences in interpretation. Patients exhibiting an Rcsf ≥ 18 mmHg/ml/minute should receive a shunt.

Over 60% of our patients, however, exhibited Rcsf values below 18 mmHg/ml/min. Since two-thirds of them showed improvement other tools are required to select patients for shunting. In a previous study¹⁷ we demonstrated the unfavorable influence of CVD on

outcome after shunting, confirming the report of Krauss et al.⁶² So we should proceed with caution when patients show signs of CVD. Because idiopathic NPH cases constitute a vulnerable group with extensive comorbidity,¹⁶ we recommend shunting if the patient can be expected to benefit from the procedure for at least 5 years.

The main result of this study is that one can rely on the clinical picture and especially the CT findings for patients with an Rcsf below the threshold of 18 mmHg/ml/min. To determine the extent to which the clinical and CT findings are typical for NPH, however, is not easy. At the end of this study we have to conclude that a gray area remains, which can only be reduced by conducting a new trial with a larger number of patients and a longer follow-up.

SUMMARY AND CONCLUSIONS

In this thesis the Dutch normal-pressure hydrocephalus study, a prospective, randomized multicenter trial involving 101 patients with NPH, is presented. **Chapter 2** contains an extensive description of the study protocol. The patient's baseline characteristics are described in this chapter as well. To quantify the symptoms a gait scale and a dementia scale were used. The gait scale consisted of a qualitative assessment of 10 aspects of gait and a quantitative part, in which the number of steps and seconds needed for a 10 meter walk were determined. The dementia scale comprised the results of four neuropsychological tests, the 10-word test, digit span, forwards and reverse, trail-making and finger tapping. The scores for the gait and dementia scale were analyzed separately but in order to obtain one value for the severity of the symptoms, they were also added; the totals comprised the "NPH scale". The third part of the NPH triad, micturition disturbances, was excluded from the scales, because this is hard to quantify. The presence of micturition disturbances was not an inclusion criterion either. The patient's level of disability was assessed with the modified Rankin scale, that was extended from a six point to a seven point scale.

A cause of the NPH syndrome could not be identified in 89 cases, the other 12 were chronic symptomatic cases. Both the gait disturbance and the cognitive decline covered the whole range from mild to severe. Sixty-seven patients were able to walk independently, whereas 34 patients could only walk with assistance or could not walk at all. Nearly all patients exhibited disturbed tandem walking and turning (defined as needing more than 2 steps). The patients often took small steps, had a wide based stride and exhibited reduced foot-floor clearance as well. Testing of the cognitive disturbances indicated that the results of the 10-word test and trail making kept pace with the total dementia scale score. The digit span and finger tapping were relatively normal, deteriorating only in severely demented patients. The cognitive decline was also assessed with the modified Mini Mental State Examination. According to this extended form of the Mini Mental State Examination with a maximum of 100 instead of 30 points, 64 % of our patients were demented. To illustrate the wide variation in severity of symptoms, 6 patients exhibited the clinical picture of akinetic mutism while five patients only showed a mild gait and cognitive disturbance.

In addition to the NPH symptomatology comorbidity was common in this population (mean age 73 years). Only 9 patients had no medical history; 44 other neurological and 190 non-neurological diseases were reported.

In **Chapter 2** the findings for 10 controls of comparable age were described. They were subjected to the same follow-up schedule except for the computed tomography and the lumbar spinal infusion test. The objective was to exclude a learning effect for the neuropsychological tests in particular. For all scales used, a significant difference between patients and controls was revealed.

In **Chapter 3** the different types of analysis used were described. The mean improvement in the various scales as well as the proportion of improved patients was used to measure outcome of shunt placement. Improvement was defined as a decrease of at least 15% in the last NPH scale score compared to the preoperative score or a decrease of one Rankin grade. Intention-to-treat analysis shows the results one year after shunting, including all comorbidity. Fifty-seven percent of the patients had improved according to NPH scale score and 59% in Rankin grades. In the efficacy analysis all known serious events that were unrelated to the NPH syndrome but interfered with neurological function were excluded to assess the results of shunting more accurately. Then the proportion of improved patients according to the NPH scale and the Rankin scale was 76% and 69%, respectively. Our results are comparable to those of other studies, with a similar follow-up time and inclusion of comorbidity. Most of the improvement occurred in the first month postoperatively. The rate of improvement was the same for both gait disturbance and cognitive decline; however, gait improved twice as much as dementia.

One of the main objectives of the study was to determine the positive and negative predictive values of the resistance to outflow of cerebrospinal fluid (Rcsf) for the results of placement of a ventriculoperitoneal shunt. For this purpose every patient underwent a lumbar spinal constant flow infusion test and, irrespective the results of the infusion test, shunt placement followed. These results were also described in **Chapter 3**. In the past an Rcsf value of 12 mmHg/ml/minute was considered the upper limit of normal. The present study showed, however, that 18 mmHg/ml/minute is a better limit with a specificity of 0.87, a positive predictive value of 0.92 and a likelihood ratio of 3.5. Because of the relatively large number of patients who improved despite an Rcsf value lower than the various cutoff values, the negative predictive values were low.

Comorbidity influenced the results of shunting negatively across the entire range of Rcsf values. Vascular diseases, both intracranial and extracranial, played a major role.

The second objective was to examine whether low or medium-high pressure shunts were more effective in reversing the signs and symptoms of NPH. The results of this study were reported in **Chapter 4**. Forty-seven of the 96 patients who could be evaluated in this study were randomized to receive a low-pressure shunt, 49 received a medium-high pressure ventriculoperitoneal Medos Hakim shunt. Intention-to-treat analysis revealed clinically relevant differences in favor of the low-pressure valve. Only the differences in dementia scale scores were statistically significant, the level of improvement with the Rankin scale scores was nearly significant ($p=0.06$). As far as the proportion of shunt responders was concerned a nearly significant difference was found for the low-pressure shunt (74% compared to 53%, $p=0.06$).

The large number of complications that occurred during the follow-up period is also described in **Chapter 4**. A remarkably large number of patients ($n=51$) suffered subdural effusions. These effusions occurred significantly more often in patients with a low-pressure than a medium-high pressure shunt ($p=0.0002$), as expected theoretically. Clinically the subdural effusions only required surgical evacuation in eight cases. These eight patients were equally spread over the low and medium-high pressure groups. For the whole study population, patients with subdural effusions improved as much as patients without effusions. We can conclude therefore that despite the large number of subdural effusions among patients with a low-pressure valve, we prefer the low-pressure shunt for the treatment of patients with NPH.

Chapter 5 contains an analysis of the role of cerebrovascular disease (CVD) in our study population. CVD was defined as the presence of at least one of the following: a history of stroke, the presence of moderate to severe white matter abnormalities or the presence of infarcts on the preoperative computed tomography. Signs of CVD were found for 45 of the 101 patients with NPH. At least one of the risk factors for CVD, such as hypertension, diabetes mellitus, cardiac disease and peripheral vascular disease, was found for 53 patients. The presence of these risk factors did not correlate either with the severity of the preoperative symptomatology, or the results of shunting. On the other hand the improvement of patients with one or more signs of CVD was significantly less after shunt placement. The proportion of improved patients in the patient group with signs of CVD was significantly smaller than among patients without CVD. White matter hypodense lesions and infarcts on computed tomography were the strongest predictors of a poor outcome. The differences in outcome could not be explained by the type of valve, because the low and medium-high pressure valves were equally divided among patients with and without CVD. Since a number of patients did improve despite extensive white matter hypodense lesions, the presence of CVD is not a reason to refrain from surgery beforehand.

The question of the role of CVD in the pathogenesis of NPH could not be answered definitively. It was thought that NPH develops as the result of an absorption deficit with an increased Rcsf, so that the intraventricular CSF pressure increases with subsequent ventricular enlargement. However, the present as well as other studies could not reveal a relationship between Rcsf on the one hand and CSF pressure, the extent of hydrocephalus and the severity of the preoperative symptomatology on the other, suggesting that an increased Rcsf is not the only pathogenic factor and that other factors play a role. One option is the presence of periventricular ischemia. The structural changes in the periventricular tissue can lead to ventricular dilation due to volume loss and changes in elasticity. An argument in support of this parenchymal hypothesis is the fact that patients with CVD showed a lower Rcsf. On the other hand the periventricular ischemic changes were irreversible for the most part, which is irreconcilable with postoperative clinical improvement. CVD probably occurs coincidentally in a sub-population of patients with NPH, without any relationship between the two conditions. Therefore the role of CVD in the pathogenesis still is not clear.

In **Chapter 6** of this thesis the diagnostic values of clinical and computed tomographic findings with respect to the influence of Rcsf measurement and CVD are considered in more detail. Both univariate analysis and multivariate analysis were used. The inclusion criteria reflected everyday clinical practice to prevent the selection of only promising surgical candidates. Therefore the clinical and computed tomographic findings could be classified as typical for or compatible with NPH. Clinical and computed tomographic findings typical of NPH, the absence of CVD and an Rcsf of at least 18 mmHg/ml/minute were considered a positive test outcome, meaning indicative of improvement after shunt placement. Clinical and computed tomographic findings compatible with the diagnosis of NPH, the presence of CVD and an Rcsf lower than 18 mmHg/ml/minute were considered a negative test result. Fifty-five patients presented with typical clinical and computed tomographic findings. Twenty-four of them also exhibited an Rcsf of at least 18 mmHg/ml/minute. Only 16 patients had four positive test results. There were significantly more improved patients as indicated by the positive test results compared to those with negative test results. This also applied for the level of improvement.

The influence of the four tests on the degree of postoperative improvement was determined with multiple regression analysis. The predictive value was in the same range, computed tomography and CVD being the most important parameters. According to logistic regression analysis Rcsf measurement appeared to be the most important independent predictor for the NPH scale and computed tomography for the

modified Rankin scale, without independent additional information by one of the other parameters. The strategy yielding the highest accuracy was to shunt patients with an Rcsf of at least 18 mmHg/ml/minute or if Rcsf was lower, those with typical clinical and computed tomographic findings.

FINAL COMMENTS

Where are we now at the end of this study? First the results of shunting. Although many patients substantially improved, the overall results of shunting were somewhat disappointing in this study population. The most important explanation seems to be the relatively moderate general condition of the patients with extensive comorbidity. Nearly 30% were in the two highest Rankin grades, 16 patients died during the follow-up of 12 months and another 17 developed severe diseases, unrelated to NPH. The extent of this comorbidity would have increased undoubtedly with a longer follow-up time. In addition there were numerous complications, some of which required new interventions. Our advice, therefore, is to be refrain from shunt placement in patients in a moderate condition, especially when signs of cerebrovascular disease (CVD) are present.

Secondly, a diagnostic test with a high specificity and sensitivity that enables reliable identification of those patients with NPH who will respond to shunt placement, was not available before. Properly, we have not found it yet. We found that Rcsf was a good predictor of good outcome for a value of at least 18 mmHg/ml/minute, but the sensitivity was low and the overall predictive values of Rcsf measurement were somewhat lower than expected in our study population. This is also explained by the relatively moderate condition of the patients. Another conclusion could be that an increased Rcsf is not the only or most important pathogenic factor for every patient. Because the lower limit of Rcsf, which implied a favorable result of shunting, was found to be higher than in previous studies, nearly two-thirds of our patients had an Rcsf below this limit of 18 mmHg/ml/minute. Nevertheless, two-thirds of this latter group improved. This study demonstrates that the indication to shunt can be based on clinical and computed tomographic findings that are typical of NPH, but the final judgment is then determined by clinical experience and not previously recorded criteria. The diagnosis NPH remains difficult and strict definition of typical clinical and computed tomographic findings are hard to give.

Which patients present problems in everyday practice? Not the patients with a truly pathognomonic form of the NPH triad, present in less than 25% of our cases. Clinically one has to be careful with patients with pronounced cognitive disturbances, especially in case of aphasia or apraxia, and only mild gait disturbances. Computed

tomographic findings of only a moderate hydrocephalus with rather much atrophy or white matter hypodense lesions present problems as well. If an increased Rcsf is found in these cases shunting can be considered. If Rcsf is lower, more data are required. Sometimes it will be appropriate to quantify the gait and cognitive disturbances during following up visits with gait scale and (modified) Mini Mental State Examination.

Further investigations are required to resolve these difficulties. More attention should be directed toward the influence of cerebrovascular disease and also toward techniques to predict good outcome in patients with CVD. Past studies of cerebral blood flow using various techniques have not revealed a good predictor of the results of shunting. Probably determination of vasomotor reactivity with the transcranial Doppler technique can play a role. A previous study of a relatively small number of patients showed promising results.³⁴ Furthermore an association between vasomotor reactivity and white matter hypodense lesions has recently been revealed.⁷ Finally, pathological studies are needed to investigate the presumed multifactorial pathogenesis. A larger number of patients should be included in a new study, with a longer follow-up. Patients with extensive comorbidity should be excluded. Such an enterprise requires international collaboration.

SAMENVATTING EN CONCLUSIES

In dit proefschrift wordt het Nederlandse normal pressure hydrocephalus (NPH) onderzoek beschreven, een prospectieve gerandomiseerde multicentrische studie bij 101 NPH-patiënten. Een uitgebreide beschrijving van het studieprotocol staat in **Hoofdstuk 2**. Ook worden hier de klinische verschijnselen van de patiënten bij opname in de studie weergegeven. Om deze in maat en getal uit te drukken hebben we een loop- en dementieschaal gebruikt. De loopschaal is opgebouwd uit een kwalitatieve beoordeling van 10 aspecten van het looppatroon en een kwantitatief deel, waarin het aantal passen en seconden wordt gemeten, dat een patiënt nodig heeft om 10 meter af te leggen. In de dementieschaal worden de resultaten opgenomen van 4 neuropsychologische tests, de 10 woorden test, trail making, digit span voor- en achteruit en vingertappen. De scores, verkregen met de loop- en dementieschaal werden afzonderlijk geanalyseerd, doch ze werden ook opgeteld tot "NPH-schaal", teneinde één getal te hebben voor de ernst van het klinische beeld. Het derde onderdeel van de NPH-triade, incontinentie voor urine, werd buiten de schaal gehouden omdat het moeilijk kwantificeerbaar is. De aanwezigheid van incontinentia urinae was ook geen inclusiecriteria. Behalve de NPH-schaal werd als handicapscore de gemodificeerde Rankin schaal gebruikt, die werd uitgebreid van een 6- tot een 7-puntsschaal.

Bij 89 patiënten ontbrak een oorzaak voor het NPH syndroom en was er dus sprake van een idiopathische NPH, 12 patiënten hadden een chronische symptomatische vorm. Zowel de loopstoornis als het cognitieve verval varieerde van mild tot zeer ernstig. Zevenenzestig patiënten konden zelfstandig lopen, 34 hadden hierbij hulp nodig of konden in het geheel niet lopen. Vrijwel alle patiënten hadden een gestoorde koorddansersgang en gestoord draaien, gedefinieerd als draaien in meer dan 2 fracties. Verder kwamen kleine passen, een breedbasische gang en sloffen veelvuldig voor. Bij het testen van de cognitieve functies hielden de prestaties op de 10 woorden test en trail making gelijke tred met de totale score op de dementieschaal. De digit span en het vingertappen bleven relatief lang gespaard en namen pas af bij de meest demente patiënten. De mate van dementie werd ook gemeten met de modified Mini Mental State Examination. Volgens deze uitgebreidere versie van de Mini Mental State Examination, met een maximum score van 100 in plaats van 30 punten, was 64%

van onze patiënten dement. Ter illustratie van de grote variatie in de ernst van het NPH syndroom: 6 patiënten hadden een beeld passend bij akinetisch mutisme en bij 5 patiënten was er slechts een discrete loopstoornis gecombineerd met gering cognitief verval.

Naast de symptomen van het NPH syndroom had deze populatie met een gemiddelde leeftijd van 73 jaar veel co-morbiditeit. Slechts 9 patiënten hadden een blanco voorgeschiedenis, in de anamnese of bij onderzoek waren er aanwijzingen voor 44 andere neurologische aandoeningen en 190 niet-neurologische ziekten.

Tevens worden in **Hoofdstuk 2** de bevindingen bij 10 controles met vergelijkbare leeftijd beschreven. Zij volgden hetzelfde schema uitgezonderd de CT-scans en de lumbale infusietest. Doel van het onderzoek bij de controlegroep was vooral het uitsluiten van een leereffect bij de neuropsychologische tests. Voor alle gebruikte schalen was er uiteraard, een significant verschil tussen de controles en NPH patiënten.

In **Hoofdstuk 3** worden de verschillende analyses beschreven, die we hebben gebruikt. Bij het meten van de uitkomst van de shuntoperatie werd de gemiddelde verbetering op de verschillende schalen bepaald, maar ook het percentage verbeterde patiënten. Verbetering werd gedefinieerd als een afname van tenminste 15% van de laatste score op de NPH-schaal ten opzichte van de preoperatieve waarde of een afname van 1 graad op de Rankin schaal. De intention-to-treat analyse geeft de uitkomst 1 jaar na plaatsen van een shunt, waarbij alle co-morbiditeit meegenomen wordt. Zevenenvijftig procent van de patiënten was verbeterd op de NPH schaal, 59% op de Rankin schaal. Bij de efficacy analyse worden alle ernstige aandoeningen, die ontstaan zijn tijdens de follow-up en die niet gerelateerd zijn aan het NPH syndroom, maar wel interfereren met het neurologisch functioneren, buiten beschouwing gelaten om zo beter het shuntresultaat te kunnen beoordelen. Volgens deze analyse was het percentage verbeterde patiënten op de NPH- en Rankin schaal respectievelijk 76 en 69%. Onze resultaten komen overeen met die van andere studies met een vergelijkbare duur van de follow-up en inclusie van co-morbiditeit. De meeste vooruitgang vond plaats in de eerste maand postoperatief, waarbij het lopen en de cognitieve stoornissen in een zelfde tempo verbeterden. De verbetering in loopscore was wel twee maal zo groot als die in de dementiescore.

Eén van de hoofddoelstellingen van het onderzoek was het bepalen van de positief en negatief voorspellende waarde van de liquor uitstroomweerstand (Rcsf) voor de resultaten van het plaatsen van een ventriculoperitoneale drain. Hiertoe onderging elke patiënt een lumbale constant flow infusietest, waarna, onafhankelijk van de uitslag van de infusietest, een shuntoperatie volgde. De resultaten hiervan worden eveneens

in **Hoofdstuk 3** beschreven. In het verleden werd een Rcsf van 12 mmHg/ml/min veelal beschouwd als bovengrens van een normale Rcsf. Uit ons onderzoek kwam echter naar voren dat 18 mmHg/ml/min een veel betere grenswaarde is met een specificiteit van 0.87, een positief voorspellende waarde van 0.92 en een likelihood ratio van 3.5. Door het relatief grote aantal patiënten, dat verbeterde, ondanks een Rcsf waarde lager dan de verschillende cut-off niveaus, waren de negatief voorspellende waarden laag.

Co-morbiditeit had een belangrijke negatieve invloed op het operatieresultaat over de gehele range van Rcsf waarden. Vasculaire pathologie, zowel intra- als extracranieel, speelde hierin een belangrijke rol.

De tweede doelstelling was het vergelijken van de effectiviteit van 2 verschillende kleptypen. De resultaten van dit onderzoek staan in **Hoofdstuk 4**. Van de 96 voor deze studie evalueerbare patiënten werden er 47 gerandomiseerd voor een low-pressure en 49 voor een medium-high pressure ventriculoperitoneale Medos Hakim shunt. Intention-to-treat analyse toonde klinisch relevante verschillen ten voordele van de low-pressure klep. Alleen de verschillen in scores op de dementieschaal waren statistisch significant, de mate van verbetering op de gemodificeerde Rankin schaal bijna ($p=0.06$). Ook als gekeken werd naar het percentage shunt-responders was er een bijna significant verschil ten faveure van de low- pressure klep (74% versus 53%, $p=0.06$).

In **Hoofdstuk 4** staan ook de vele complicaties beschreven, die optraden tijdens de follow-up. Er was een opmerkelijk groot aantal patiënten ($n=51$), bij wie subdurale effusies werden gezien. Zoals theoretisch verwacht traden deze significant vaker op bij patiënten met een low- dan met een medium-high pressure shunt ($p=0.0002$). Klinisch waren deze effusies slechts bij 8 patiënten zodanig symptomatisch dat operatieve verwijdering nodig was. Deze patiënten waren gelijkmatig verdeeld over de beide kleptypen. In de gehele onderzoekspopulatie deden de patiënten met subdurale effusies het ook niet slechter dan zonder effusies. Onze conclusie is dan ook, dat, ondanks het grote verschil in subdurale effusies ten nadele van de low pressure klep, de voorkeur uitgaat naar een low pressure klep bij de operatieve behandeling van patiënten met NPH.

Hoofdstuk 5 bevat een analyse van de rol van cerebrovasculaire ziekte (CVZ) in onze studiepopulatie. CVZ werd gedefinieerd als de aanwezigheid van ten minste één van de volgende drie verschijnselen: een stroke in de voorgeschiedenis, de aanwezigheid van matig tot ernstige witte stof afwijkingen of van infarcten op de preoperatieve CT-scan van de hersenen. Tekenen van CVZ werden gevonden bij 45 van de 101 patiënten met NPH. Bij 53 patiënten was er tenminste één van de risicofactoren voor

hart- en vaatziekten, te weten hypertensie, diabetes mellitus, hartziekten en perifeer vaatlijden. De aanwezigheid van deze risicofactoren bleek echter niet te correleren met de ernst van het preoperatieve beeld, noch met de resultaten van het aanbrengen van een shunt. Daarentegen vertoonden patiënten met één of meer tekenen van CVZ significant minder verbetering postoperatief. Ook was het percentage verbeterde patiënten in de groep van patiënten met CVZ significant kleiner dan in de groep zonder CVZ. Witte stof afwijkingen en infarcten op de preoperatieve CT scan waren de sterkste voorspellers van een slecht resultaat. De verschillen in uitkomst konden niet verklaard worden door het kleptype, omdat de low- en medium-high kleppen gelijkelijk verdeeld waren over de patiënten met en zonder CVZ. Daar een aantal patiënten met uitgebreide witte stof afwijkingen toch goed verbeterde, kan de aanwezigheid van CVZ geen reden zijn om op voorhand van een operatie af te zien.

Op de vraag of CVZ een rol speelt in de pathogenese van NPH kunnen argumenten voor en tegen genoemd worden. De gedachte was, dat NPH ontstaat door een afvloedbelemmering van de liquor met een verhoogde Rcsf, waardoor de liquordruk in de ventrikels toeneemt met als gevolg ventrikeldilatatie. Door ons en andere onderzoekers kon echter geen relatie worden aangetoond tussen Rcsf enerzijds en de liquordruk, de mate van hydrocephalus en de ernst van het klinisch beeld preoperatief anderzijds. Dit suggereert, dat een verhoogde Rcsf niet de enige pathogenetische factor is en dat ook andere factoren een rol spelen. Eén kandidaat hiervoor is de aanwezigheid van periventriculaire ischemie. De structuurverandering van het periventriculaire weefsel kan via volumeverlies en verandering in elasticiteit ook leiden tot ventrikelverwijding. Een argument voor deze parenchymateuze hypothese is dat de patiënten met CVZ een lagere Rcsf hadden. Anderzijds lijken de periventriculaire ischemische veranderingen grotendeels irreversibel, hetgeen niet goed te rijmen is met afname van de ventrikelgrootte en klinische verbetering postoperatief. Het is dus ook zeer wel mogelijk dat er een subgroep is van NPH patiënten met CVZ zonder dat er een etiologisch verband tussen beiden bestaat. De rol van CVZ in de pathogenese is dus nog niet duidelijk.

In **Hoofdstuk 6** van dit proefschrift wordt ingegaan op de diagnostische waarde van klinische en CT-scan bevindingen ten opzichte van de invloed van CVZ en Rcsf-meting. Hierbij werden univariate en multivariate analyse technieken gebruikt. Met de inclusiecriteria van deze studie hebben we zoveel mogelijk de praktijk van alledag trachten te volgen om te voorkomen dat alleen briljante operatiekandidaten geïncludeerd zouden worden. Derhalve was het mogelijk om zowel het klinische beeld als de CT bevindingen te classificeren als typisch voor NPH, dan wel passend bij NPH. Een typische klinisch beeld, typische CT-bevindingen, de afwezigheid van CVZ en een

Rcsf ≥ 18 mmHg/ml/min werden als een positieve testuitslag beschouwd, d.w.z. indicatief voor verbetering na het aanbrengen van een shunt. Klinische en CT-afwijkingen, die kunnen passen bij NPH, de aanwezigheid van CVZ en een Rcsf < 18 waren een negatieve testuitslag. Typische CT- en klinische bevindingen waren aanwezig bij 55 patiënten, 24 hiervan hadden ook een Rcsf ≥ 18 , slechts 16 patiënten hadden 4 positieve testuitslagen. Het percentage verbeterde patiënten was voor alle positieve testuitslagen significant beter dan voor negatieve. Dit gold ook voor de mate van verbetering.

Met behulp van regressie analyse werd het effect van de 4 tests op de mate van postoperatieve verbetering berekend. De voorspellende waarde lag in dezelfde orde van grootte met CT en CVZ als belangrijkste parameters. Uit logistische regressie bleek, dat Rcsf de belangrijkste onafhankelijke voorspeller was op de NPH schaal en de CT-scan op de Rankin schaal, zonder onafhankelijke aanvullende informatie van één van de overige factoren. De shuntstrategie met de hoogste voorspellende waarde bleek om patiënten een shunt te geven bij een Rcsf ≥ 18 mmHg/ml/min, of als Rcsf kleiner was, bij typische klinische en CT- bevindingen.

SLOTOPMERKINGEN

Waar zijn we nu aan het eind van deze studie? Als eerste iets over de operatieresultaten. Alhoewel veel patiënten aanzienlijk zijn verbeterd, zijn de operatieresultaten over de gehele populatie genomen wat tegengevallen. De belangrijkste verklaring hiervoor lijkt de relatief matige algemene conditie van de patiënten met veel co-morbiditeit. Bijna 30% verkeerde in de hoogste 2 Rankin klassen, 16 patiënten zijn tijdens de follow-up van 12 maanden overleden en nog eens 17 ontwikkelden ernstige, niet aan NPH gerelateerde aandoeningen. Bij een langere follow-up duur zou de omvang van deze co-morbiditeit en mortaliteit ongetwijfeld zijn toegenomen. Daarnaast was het aantal complicaties van de shuntoperaties niet gering, waarbij regelmatig nieuwe ingrepen noodzakelijk waren. Derhalve is ons advies terughoudend te zijn met shuntoperaties bij patiënten in een matige conditie, zeker als er ook tekenen zijn van cerebrovasculaire ziekte.

Ten tweede was er tevoren geen goede test met een hoge specificiteit en sensitiviteit waarmee het operatieresultaat betrouwbaar kon worden voorspeld. Eigenlijk hebben we die nog steeds niet. We vonden, dat Rcsf een goede voorspeller van een goede outcome was bij een waarde van tenminste 18 mmHg/ml/min, maar de sensitiviteit was laag en over het geheel is de voorspellende waarde van de Rcsf ook in onze studiepopulatie enigszins lager dan verwacht. Een verklaring hiervoor is

eveneens de relatief “slechte” patiëntenpopulatie met veel co-morbiditeit. Een andere conclusie zou kunnen zijn, dat een gestoorde Rcsf klaarblijkelijk niet bij iedere patiënt de enige of belangrijkste pathogenetische factor is.

Omdat de grenswaarde van de Rcsf, waarboven met voldoende zekerheid een gunstig operatieresultaat kon worden voorspeld, hoger lag dan in andere studies, had ruim 60% van de patiënten een Rcsf onder de grenswaarde, van wie tweederde desondanks verbeterde. Weliswaar werd aangetoond, dat de indicatie voor het aanbrengen van een shunt kan worden gesteld als er voor NPH typische klinische en CT-bevindingen zijn, doch de beoordeling daarvan berustte op onze klinische expertise en niet op vooraf vastgelegde criteria. De diagnose NPH blijft moeilijk en harde criteria voor typische klinische en CT criteria zijn moeilijk te geven.

Welke patiënten leveren nu in de praktijk de meeste problemen op? Niet de patiënten met een klassiek klinisch beeld en de daarbij behorende CT bevindingen. Klinisch moet men vooral oppassen voor patiënten met geprononceerde cognitieve veranderingen hebben, vooral als er corticale functiestoornissen zijn, met een relatief milde loopstoornis. Op de CT-scan vormen de patiënten een probleem, die slechts een matige hydrocephalus hebben met vrij veel atrofie of witte stof afwijkingen. Als bij dergelijke patiënten een verhoogde Rcsf wordt gevonden, lijkt een operatie geïndiceerd. Is de Rcsf lager, dan zijn toch extra gegevens nodig. Soms kan het zinvol zijn bij deze patiënten loopstoornis en cognitief verval “kwantitatief” te vervolgen, bijvoorbeeld met loopscore en (gemodificeerde) Mini Mental State Examination.

Om deze problemen verder op te lossen is verder onderzoek nodig. Meer aandacht moet worden besteed aan de invloed van cerebrovasculaire ziekte op de pathogenese. Daarnaast zou onderzocht moeten worden hoe voorspeld kan worden welke patiënt met cerebrovasculaire ziekte wel gebaat is bij een shunt en welke niet. In het verleden heeft onderzoek van de cerebrale bloeddoorstroming met verschillende technieken niet veel opgeleverd als voorspeller van het operatieresultaat. Mogelijk is een rol weggelegd voor bepaling van de vasomotore reactiviteit met behulp van transcranieel Doppler onderzoek. Een eerdere studie bij een relatief klein aantal NPH patiënten toonde veelbelovende resultaten.³⁴ Daarnaast werd recent een associatie tussen vasomotore reactiviteit en witte stof afwijkingen aangetoond.⁷ Verder is er, gezien de vermoedelijk multifactoriële pathogenese, ook behoefte aan meer pathologisch anatomisch onderzoek.

In een nieuw onderzoek zou een groter aantal patiënten moeten worden opgenomen, de follow-up duur zou langer moeten zijn en patiënten met veel co-morbiditeit zouden moeten worden uitgesloten. Een dergelijke onderneming vereist internationale samenwerking.

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Curriculum Vitae

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