Neuropsychological Effects of Shunt Treatment in Idiopathic Normal Pressure Hydrocephalus

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OBJECTIVE: To prospectively evaluate the effects of shunting on the neuropsychological performance of patients with idiopathic normal pressure hydrocephalus (INPH), to compare their performance with that of healthy individuals, and to estimate the predictive utility of putatively important factors.

METHODS: A consecutive series of 47 patients with INPH underwent neurological, radiological, and neuropsychological examinations before and 3 months after shunt surgery. The same neuropsychological tests, measuring simple and target reaction times, dexterity, memory and learning, working memory, and aspects of executive functioning, were also administered to 159 healthy individuals.

RESULTS: Performance on all neuropsychological tests, except Simple Reaction Time and Digit Span, significantly improved after surgery, with more severe functional deficits showing greatest improvement. Age, education, duration, vascular comorbidity, sex, and onset symptom all failed to predict the neuropsychological effects of treatment. Despite improvement 3 months after shunt surgery, INPH patients were still outperformed by healthy individuals.

CONCLUSION: Most of the wide range of neuropsychological functions that are affected by INPH are markedly improved by shunt treatment, but not completely restored.

KEY WORDS: Idiopathic normal pressure hydrocephalus, Neuropsychology, Outcome, Performance, Prospective study, Shunt surgery, Treatment effect

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Idiopathic normal pressure hydrocephalus (INPH) is a condition of disturbed cerebrospinal fluid (CSF) dynamics, the causes of which are not known. It is clinically characterized by progressive impairment of gait and balance, cognitive deterioration, and urinary incontinence in conjunction with an enlarged ventricular system and normal intracranial pressure.

The success rate of shunt surgery in reported series has ranged from 30 to 96% (22, 31, 45, 56). Reported long-term effects of shunting also vary considerably between studies (26–50%) (30, 36, 53). The neuropsychological characteristics of INPH and the cognitive effects of shunting have been much debated during recent years (17, 37). Reported improvement in neuropsychological functions after surgery have ranged from no statistically significant improvement to improvement rates of 70% (27, 44, 47, 51).

ABBREVIATIONS: CSF, cerebrospinal fluid; **HI**, healthy individual; **INPH**, idiopathic normal pressure hydrocephalus

We recently showed that the preoperative neuropsychological deficits in INPH are wide-ranging, interrelated, associated with neurological signs, and aggravated by vascular comorbidity (24). The aims of this prospective study were to evaluate the effects of shunting on neuropsychological performance in INPH patients and to estimate the predictive utility of putatively important factors.

PATIENTS AND METHODS

Patients

Fifty-six consecutive patients with INPH were preoperatively examined and reevaluated postoperatively at the Hydrocephalus Research Unit, Sahlgrenska University Hospital, between January 1, 1999, and December 31, 2006.

The diagnosis of INPH was based on the presence of typical gait disturbance (6, 46, 50), either organic mental symptoms (35, 54) or urinary incontinence (2), enlarged ventricles on computed tomography or magnetic resonance imaging scans (Evans' index >0.30), a lumbar CSF pressure below 18 mmHg, and an open aqueduct as evidenced by magnetic resonance imaging and/or radionuclide cisternography. The diagnosis also required an insidious onset and no evidence of antecedent causes of secondary hydrocephalus.

A neurological examination was performed according to standard procedures at our unit (6, 34, 55) and included the assessment of dementia (by means of the Mini-Mental State Examination [18]), gait, balance, incontinence, and daily hours of sleep. Vascular risk factors (hypertension, diabetes, and cardiovascular disease) were registered as present or not present. A neuropsychological examination was also performed (24).

All patients subsequently received ventriculoperitoneal shunts and were re-examined 3 months postoperatively using the same methods.

The valves used were Delta shunts (Medtronic PS Medical, Goleta, CA) (i.e., fixed valves, n = 18), Strata programmable valves (n = 27) (Medtronic PS Medical), and Codman Hakim programmable valves (Johnson & Johnson Co., Raynham, MA) (n = 11). In cases of unsatisfactory clinical improvement after surgery, the valves were checked using either the radionuclide shunt function test (58) or a computerized infusion test. Dysfunctioning valves were replaced, and in cases of working shunts associated with little or no clinical improvement, valves were adjusted to enhance treatment response.

Valve opening pressure was adjusted in 10 patients (lowered in 9 and raised in 1), and consequently, the postoperative examination was postponed for 3 months. Of these, four patients had a full-scale reexamination; three patients were clinically improved after several adjustments but could not be reexamined according to the protocol; and three patients had undetermined outcome and no complete reexamination was performed. Thus, the latter six patients were excluded. Eight patients experienced shunt-related problems. Of these, two had subdural hematomas and were reexamined according to the protocol 3 months after treatment (one revision, one adjustment), and five patients had mechanical shunt problems which required reoperation. Of the latter five patients, three were reevaluated according to the protocol, whereas two experienced repeated complications and were excluded because they could not be neuropsychologically reevaluated. One patient was excluded owing to uncertain shunt function at the time of reexamination. Thus, nine patients were excluded owing to lack of complete reexaminations, leaving 47 patients in the study.

A comparison group comprising 159 healthy individuals (HI) with a comparable age distribution was recruited from senior associations and church organizations. Participants voluntarily underwent neuropsychological testing in the spring of 2006. Individuals with neurological disorders were excluded, whereas those with stable medical conditions (e.g., successfully treated diabetes, hypertension, or hypothyreosis) and/or minor psychiatric disorders (e.g., mild symptoms of anxiety or depression and/or self-reported use of antidepressants [selective serotonin reuptake inhibitors only] or mild tranquilizers) were included. Information regarding the presence of vascular risk factors among the HIs was not recorded. Demographic characteristics of patients and HIs are shown in *Table 1*, and the preoperative clinical characteristics of the patients are presented in *Table 2*.

Neuropsychological Methods

All of the INPH patients were examined by the same neuropsychologist (PH). The formal testing was preceded by a clinical interview to acquaint the patient with the clinician and the situation. The following tests were administered: Simple Reaction Time, Target Reaction Time, Grooved Pegboard, Tracks Task, Rey Auditory Verbal Learning Test, Swedish Stroop Test, and Digit Span.

Simple Reaction Time is a computerized task developed at our unit that measures mean reaction time. The patient is instructed to fixate on a white cross on a black screen and to press the space bar as quickly as possible when the screen turns white. There are 20 screen changes, and the length of the fixation intervals varies randomly between 2 and 6 seconds (this task was not included in the assessment of HIs).

Target Reaction Time measures mean reaction time in milliseconds for 20 randomly appearing targets. The fixation conditions are identical to those in the previous task, and the patient is also instructed to press the space bar as quickly as possible when the screen turns white (target), but to avoid pressing if it turns red (nontarget). The same number of nontargets and targets are presented in each session, and the order of presentation is randomized. The two reaction time tasks were developed using E-Prime (Psychology Software Tools, Inc., Pittsburgh, PA) and were administered on standard computers.

The Grooved Pegboard (Lafayette Instrument Co., Lafayette, IN) measures manual dexterity as time to fit 25 pegs into holes with randomly positioned slots. The test is performed first with the dominant hand, followed by a trial with the nondominant hand. The score represents the time in seconds to complete both trials.

The Tracks Task, originally constructed by Alan Baddeley (4) as the motor half of a dual task, measures motor speed in a task requiring the patient to cross squares in an order indicated by connecting lines (the score is the number of squares in 1 minute).

The Rey Auditory Verbal Learning Test (48) assesses verbal learning and memory. Scores represent the total number of words recalled over five learning trials and the number of words remembered after 30 minutes.

The Swedish Stroop Test (23) measures naming speed, response selection, and inhibition. It requires the patient to name the colors (blue, red, green, or yellow) of 100 rectangles as fast as possible, and then to name the printed color of 100 incongruent color words (e.g., the word "blue" printed in red). The scores are the number of seconds to complete each trial (color naming and interference) and the difference in seconds between the two trials (reflecting the extra time needed to select the correct response in the interference condition).

TABLE 1. Demographic characteristics of idiopathic normal pressure hydrocephalus patients and healthy individuals[a]

Demographic characteristics	INPH (n = 47)	HI (n = 159)
Age, median (range)	73 (24–84)	73 (50–87)
Sex, male/female (%)	47/53	46/54
Education (yr), median (IQR)	11 (7–14)	13 (10–17)
Living conditions (%)		
At home without assistance	60	100
At home assisted by spouse or relatives	21	
At home assisted by home service	6	
Service flat	6	
Nursing home or hospital	6	

[a] INPH, idiopathic normal pressure hydrocephalus; HI, healthy individual; IQR, interquartile range.

TABLE 2. Symptoms, signs, and comorbidity in idiopathic normal pressure hydrocephalus[a]

Gait disturbance (100%)	No. or %
0 Normal	0%
1 Insecure but unaided	60%
2 Cane	15%
3 Bimanual support	17%
4 Living support	6%
5 Wheelchair	2%
Balance disturbance (100%)	
0 Normal	0%
1 Unstable	30%
2 Romberg <60 s	8%
3 Romberg <30 s	43%
4 Unable	19%
Incontinence (100%)	
0 Normal	20%
1 Urgency	24%
2 Occasional leakage	22%
3 Always diapers	28%
4 Double incontinence	6%
Cognition	
MMSE, median (range)	25 (7–29)
Daily need of sleep	
Time (h), median (range)	9.5 (6–18)
Comorbidity (%)	
Hypertension	21%
Cardiovascular disease	26%
Diabetes	11%
Combinations	43%

[a] MMSE, Mini-Mental State Examination.

The Digit Span Test, from the Wechsler Adult Intelligence Scale III (Harcourt Assessment, Inc., San Antonio, TX), assesses short-term or working memory by means of forward and backward repetition of series of digits. Scores correspond to the number of digits in the longest series under each condition. A summary score (Wechsler Adult Intelligence Scale score) is also calculated and represents the total number of correctly repeated series under both conditions.

The rationale for the selection of the specific instruments has been described earlier (24). Owing to changes in examination routines through the years, not all of the patients were assessed with all of the above tests (actual numbers are presented in *Table 3*). The HI group was tested in neutral settings by one of four psychology students, who were trained and supervised by PH.

Statistical Analysis

Nonparametric statistical methods were used in all analyses of ordinal variables and of continuous quantitative variables as a result of nonsymmetrical distributions and/or substantially larger variances among patients than among the HIs. The Spearman rank correlation coefficient (ρ) was used to estimate associations between variables. The Wilcoxon-Mann-Whitney *U* test was used for comparisons between INPH patients and HIs and between subgroups of patients, whereas the Wilcoxon signed-rank test was used for comparisons between pre- and postoperative results of the INPH patients.

The predictive utility of the selected variables was estimated by means of ρ or the Wilcoxon-Mann-Whitney *U* test, depending on the nature of the variables. The Bonferroni-Holm step-down test (25, 26) was applied to adjust for multiple pairwise comparisons.

The numerical differences between pre- and postoperative measurements were used for the classification of patients as improved, unchanged, or worsened (*Table 3*). The performance of patients before and after surgery, as well as the magnitude of postoperative changes, is expressed as percentage of the median performance of the HIs. To establish the proportional performance of patients relative to HIs on tests with time scores (Target Reaction Time, Grooved Pegboard, and the Stroop variables), the values were recalculated as units per second. It should be noted that median values of individual changes (*Table 3*; *Fig. 2*) are not mathematically identical to the differences between pre- and postoperative median values of the total group of INPH patients (*Fig. 1*). Statistical analyses were performed with SPSS 13.0 for Windows (SPSS Inc., Chicago, IL).

RESULTS

The INPH patients showed statistically significant improvement in all applied tests except for the Simple Reaction Time, Digit Span forward, and the Digit Span Wechsler Adult Intelligence Scale score (*Table 3*). The greatest proportion of patients showed improvement on the Stroop (82–91%) and Grooved Pegboard (86–90%) tests, whereas the lowest proportion of patients improved on the Digit Span forward (26%) and backward (44%) tests.

The preoperative performance of INPH patients was below that of HIs on all tests, ranging from 38 to 88% of the median performance of HIs. After surgery, the median performance of INPH patients improved on all tests except for Digit Span and ranged from 62 to 94% of the median performance of HIs (*Fig. 1*).

Functions that were more severely impaired before surgery tended to improve more than milder deficits. There was a significant negative correlation ($r_s = -0.80$, n [i.e., the number of tests] = 9, $P < 0.05$) between the median preoperative performance levels of the different tests and their median magnitude of improvement after treatment (*Fig. 2*).

The proportions of improved, unchanged, and worsened results on the individual tests and clinical variables are presented in the rightmost column in *Table 3*. Information regarding the number of individuals who improved on each of the nine neuropsychological measures (*Figs. 1* and *2*) is presented in *Table 4*.

The patterns of associations between the neuropsychological variables was different for the INPH patients pre- and postsurgery than for the HI group. Several significant correlations between the tests findings in the INPH patient group (both pre- and postoperatively) were not seen in the HI group. The strength of the majority of inter-test correlations was lower

TABLE 3. Neuropsychological performance and neurological signs in idiopathic normal pressure hydrocephalus patients before and after shunt surgery and test results for healthy individuals (not included in the statistical analyses)[a]

	HI (n = 159)	INPH before surgery	INPH 3 mo after surgery	INPH difference	*P* value	Change I/U/W
Neuropsychological test results, median (IQR)						
MMSE (n = 46)		25.5 (23–28)	28 (25–29)	1 (0–3)	<0.001[b]	74/6/20
Reaction time, ms						
Simple (n = 43)		285 (246–342)	266 (236–317)	12 (–23 to 59)	0.12[b]	56/0/44
Target (n = 41)	462 (428–498)	527 (483–706)	492 (420–658)	43 (–8 to 109)	<0.001[b]	74/0/26
Tracks (n = 42)	80 (76–90)	58 (51–72)	66 (54–78)	7 (0–13)	<0.0001[b]	74/12/14
Grooved Pegboard (n = 41)						
Dominant hand	78 (69–91)	121 (104–163)	106 (88–127)	16 (5–44)	<0.0001[b]	86/2/12
Nondominant hand	93 (80–113)	162 (117–259)	135 (98–186)	26 (5–52)	<0.0001[b]	86/2/12
Sum of both hands	172 (151–201)	293 (234–394)	240 (190–312)	42 (16–92)	<0.0001[b]	90/0/10
Digit Span (n = 40)						
Forward	6 (5–7)	5 (5–6)	6 (5–6)	0 (0–1)	0.11[b]	26/58/16
Backward	4 (4–5)	4 (3–4)	4 (3–4)	0 (0–1)	<0.01[b]	44/46/10
WAIS score	13 (11–15)	10 (8–12)	10 (9–13)	1 (–1 to 1)	0.02[b]	57/16/27
Rey AVLT (n = 46)						
Sum of trials 1–5	42 (35–50)	28 (20–34)	35 (24–42)	6 (2–11)	<0.0001[b]	85/2/13
Delayed recall	8 (6–11)	3 (1–5)	5 (2–8)	1 (1–4)	<0.001[b]	66/18/16
Stroop tasks, time (s)						
Color naming (n = 25)	67 (60–75)	98 (84–130)	85 (71–106)	12 (5–18)	<0.001[b]	88/4/8
Interference task (n = 22)	128 (108–150)	249 (144–305)	166 (124–264)	38 (5–78)	<0.01[b]	91/0/9
Response selection (n = 22)	62 (46–77)	135 (58–198)	81 (49–148)	25 (8–74)	<0.01[b]	82/0/18
Neurological signs, median (IQR)						
Gait						
Clinical grading (n = 47)		2 (2–4)	2 (1–3)		<0.0001[c]	60/38/2
10 m, no. of steps (n = 43)		24 (18–39)	18 (16–22)	4 (1–14)	<0.0001[b]	90/5/5
10 m, time (s) (n = 43)		14 (10–24)	10 (9–13)		<0.0001[b]	79/14/7
Balance (n = 46)		3 (1–3)	1 (1–3)		<0.001[c]	35/63/2
Incontinence (n = 46)		3 (2–5)	1 (1–2)		<0.0001[c]	68/28/4
Hours of daily sleep (n = 42)		9.5 (8–12)	8 (7–9)	1 (0–3)	<0.0001[b]	53/40/7

[a] HI, healthy individual; I, improved; INPH, idiopathic normal pressure hydrocephalus; IQR, interquartile range; MMSE, Mini-Mental State Examination; U, unchanged; W, worse; WAIS, Wechsler Adult Intelligence Scale; AVLT, Auditory Verbal Learning Test.
[b] Wilcoxon signed rank test.
[c] Sign test.

postsurgery, and the matrix thus coincided more closely with that of the HI group (*Table 5*).

The changes in test performance and the changes in the clinical variables of gait, incontinence, and hours of sleep were also subjected to correlation analyses. There were significant associations between reduction of sleep and improvement in dexterity, learning, and color naming (r_s = 0.34, 0.33, and 0.52, respectively), and between the improvement in gait and the Stroop variables of Interference and Selection (r_s = 0.60 and 0.54 for the time, r_s = 0.55 and 0.49 for the number of steps).

Among the background variables of age, education, and disease duration, age correlated significantly with the magnitude of improvement on the Grooved Pegboard and Stroop color naming tests, whereas education was negatively correlated with improvement on the Grooved Pegboard test. No other statistically significant correlations were found (*Table 6*).

The predictive utility of the categorical variables, including vascular risk factors (presence/absence, n = 20 and n = 27, respectively), onset symptom (gait disturbance/cognitive deterioration, n = 13 and n = 11), and sex (male = 22/female = 25),

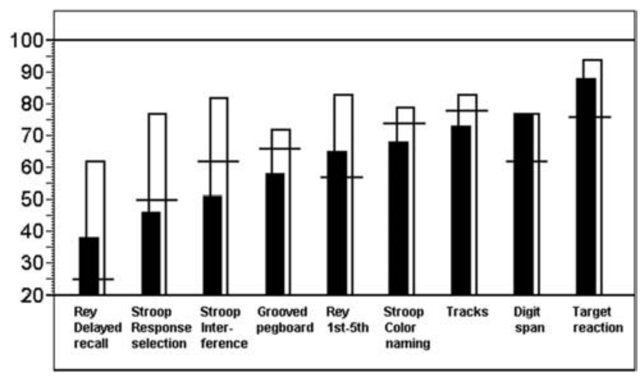

FIGURE 1. *Graph showing performance before (*black bars*) and 3 months after shunt surgery (*white bars*), expressed in percentages of median performance for healthy individuals (HI) (100%). The 5th centile for HI on each variable is represented by a* short horizontal line. *Only tests with data from HI and patients with idiopathic normal pressure hydrocephalus (INPH) are included. The Grooved Pegboard and Digit Span tests are represented by the composite scores.*

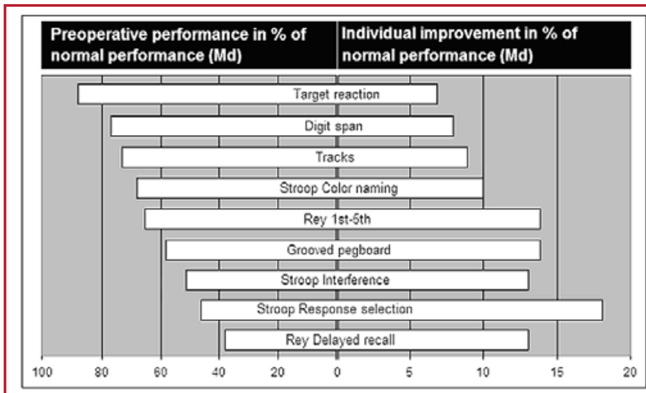

FIGURE 2. *Graph showing performance of INPH patients before surgery and the magnitude of change, both are expressed in percentages of median performance of HIs.* Md, *median.*

was also evaluated. There were no statistically significant differences between the subgroups.

DISCUSSION

In INPH, the CSF dynamic disturbance and its corollaries, the expansion of the ventricular system, and the resultant blood flow decrements and metabolic disturbance of the circumventricular tissue (1, 11, 12, 33, 41) affect several subcortical structures and subcortical-cortical circuits. Consequently, neurological functions like movement, tonus, and posture, but also more complex functions (e.g., purposeful acquisition and retention of new information, willed planning, initiation and monitoring of motor or mental processes, problem-solving, decision-making,

TABLE 4. Number of idiopathic normal pressure hydrocephalus patients (n = 47) showing improvement on 0 to 9 of the neuropsychological variables

	No. of improved tests									
	0	1	2	3	4	5	6	7	8	9
No. of patients	2	1	1	4	7	11	10	5	3	3

etc.) that depend on the integrity of the constituents of functional networks and their connections, may be impaired. The simultaneous presence of gait disturbance, cognitive deterioration, and incontinence seen in most hydrocephalic patients suggests a common pathophysiological mechanism (34, 37). This notion is reinforced by neuropsychological studies showing that multiple and diverse functions are affected by INPH, including vigilance; psychomotor speed; attention and concentration; memory and learning; visuoperceptual, spatial, and constructive ability; arithmetic, reading, and writing; problem-solving; conceptualization; abstract reasoning; and executive functions (5, 13–15, 28, 29, 38, 40, 42, 43, 51, 52, 54). Further evidence stems from reports on strong and frequent associations not only between neuropsychological tests, but also between such tests and assessments of gait and balance disturbance, incontinence, and increased daily sleep (24, 40). The presence of vascular risk factors and vascular lesions affecting the same subcortical regions have been shown to increase the severity of neuropsychological deficits seen in INPH (24) and to reduce the benefit of shunt surgery (7, 49).

Neuropsychological Changes after Shunt Surgery

Most of the tests applied in this study discriminate well between INPH patients before surgery and HIs (24). In the present study, we found that the same tests also distinguished between pre- and postoperative performance (*Table 3*).

Furthermore, there was a negative correlation between preoperative performance levels and the magnitude of improvement on different tests. A reasonable explanation for this is that functions that are more heavily dependent on the integrity of the structures and circuits that are most affected by metabolic (as opposed to structural) changes as a result of INPH are those that will also improve more after the abolition of the CSF dynamic disturbance causing these changes. This view is supported by the immediate response to the CSF tap test (57).

However, our findings also clearly demonstrate that the neuropsychological functions are not fully restored and that the INPH patients were still outperformed by HIs on all of the tests included in *Table 5* (Wilcoxon-Mann-Whitney, all P values < 0.05), except for the Target Reaction Test. We find it likely that these remaining deficits reflect irreversible changes attributable to hydrocephalus, some of which have been described in neuropathological studies (3, 11, 12).

Our own clinical expectations and the information we provide to INPH patients and their relatives before surgery should be tem-

TABLE 5. Correlation matrices for idiopathic normal pressure hydrocephalus patients before and after surgery and for healthy individuals[a]

	TR	Tracks	GP	DS	R1–5	Rdel	SC	SI	SS
INPH before surgery									
Target Reaction	1								
Tracks	–0.51[b]	1							
Grooved Pegboard	0.55[b,d]	–0.73[b,d]	1						
Digit Span	–0.34[c,d]	0.61[b,d]	–0.46[b]	1					
Rey 1st–5th	–0.40[b,d]	0.81[b,d]	–0.62[b,d]	0.55[b,d]	1				
Rey delayed		0.64[b,d]	–0.42[b,d]	0.44[b,d]	0.73[b]	1			
Stroop color	0.75[b,d]	–0.82[b,d]	0.91[b,d]	–0.59[b,d]	–0.71[b,d]		1		
Stroop interference	0.64[b]	–0.60[b]	0.79[b]		–0.62[b,d]		0.88[b]	1	
Stroop selection	0.60[b]	–0.56[b]	0.75[b]		–0.60[b]		0.84[b]	0.99[b,d]	1
INPH after surgery									
Target Reaction	1								
Tracks	*–0.54*[b,d]	1							
Grooved Pegboard	0.44[b]	–0.60[b]	1						
Digit Span		0.54[b]	–0.47[b,d]	1					
Rey 1st–5th	–0.36[c]	0.60[b]	–0.45[b]	0.45[b]	1				
Rey delayed		0.41[b]	–0.33[c]	0.40[c]	0.79[b,d]	1			
Stroop color	0.60[b]	–0.68[b]	0.83[b]	–0.49[c]	–0.51[c]		1		
Stroop interference	0.65[b,d]	–0.68[b]	0.84[b,d]	–0.48[c,d]	–0.62[b,d]		0.90[b,d]	1	
Stroop selection	0.66[b,d]	–0.67[b,d]	0.83[b,d]		–0.63[b,d]		0.85[b,d]	0.98[b]	1
Healthy individuals									
Target Reaction	1								
Tracks	*–0.35*[b]	1							
Grooved Pegboard		–0.49[b]	1						
Digit Span				1					
Rey 1st–5th		0.30[b]	–0.32[b]		1				
Rey delayed			–0.35[b]		0.77[b]	1			
Stroop color		–0.42[b]	0.31[b]				1		
Stroop interference		–0.37[b]	0.34[b]	–0.46[b]			0.63[b]	1	
Stroop selection				–0.42[b,d]				0.91[b]	1

[a] TR, Target Reaction; GP, Grooved Pegboard; DS, Digit Span; R1–5, Rey 1st to 5th; Rdel, Rey delayed; SC, Stroop color; SI, Stroop interference; SS, Stroop selection; INPH, idiopathic normal pressure hydrocephalus.
[b] $P < 0.01$.
[c] $P < 0.05$.
[d] Correlation coefficients that are equal to or larger than corresponding coefficients in the other two conditions. Other values represent nonsignificant correlations and/or coefficients of <0.30.

pered in accordance with these findings. The few studies of neuropsychological effects of shunt treatment in INPH have generally presented positive effects. However, the ways of defining change have differed among authors. To compare our findings with some of the more well-known reports, we subjected our data to the same analyses as those used in other studies. Raftopoulos et al. (45) used the ratio between the postoperative result and the sum of the pre- and postoperative results (i.e., post/[pre + post]) to calculate the "percent change." They found 14 (66.6%) of their 21 patients to be improved 1 year after surgery (defining improvement as a quotient exceeding 0.55). The corresponding proportion in our study is 80.8% (38 of 47 patients). Two more recent studies have used an improvement criterion corresponding to a positive change of 1 standard deviation of HI on 50% of the tests, or a 4-point change on the Mini-Mental State Examination at least 3 months after surgery. The proportions of successful cases in these series were 52% (22 of 42 patients) (51) and 60% (6 of 10 patients) (16), respectively. The corresponding proportion in our group of patients was 51% (24 of 47 patients), i.e., similar to the finding in the larger of the two series.

TABLE 6. Changes in neuropsychological test results and their relations to age, education, and disease duration

Neuropsychological test	Age	Education	Duration
Target Reaction	–0.07	–0.04	0.18
Tracks	0.14	–0.06	0.00
Grooved Pegboard	0.60[a]	–0.36[b]	0.08
Digit Span	0.22	0.29	0.00
Rey 1st–5th	0.04	0.25	–0.10
Rey delayed	0.12	0.01	–0.28
Stroop color	0.51[b]	–0.12	0.19
Stroop interference	0.32	–0.18	0.11
Stroop response selection	0.27	–0.16	0.02

[a] $P < 0.01$.
[b] $P < 0.05$.

Associations among Deficits before and after Surgery

There were many pronounced correlations among the different neuropsychological tests, particularly in relation to preoperative assessments. A probable explanation for this is the multiregionality of the disease process, which contributes to the variability of all the functions tested and thereby creates or strengthens associations among them. This phenomenon has been labeled "dedifferentiation." This term is used in research concerning cognitive development and refers to development from a relatively undifferentiated state of early childhood through a gradual differentiation of intellectual functions and then, at a much later stage, to an increasing dedifferentiation of advanced aging (10).

The dedifferentiation in INPH is not restricted to neuropsychological performance. We have recently presented findings regarding associations between neuropsychological test results and the severity of gait and balance disturbance, incontinence, and increased daily sleep among INPH patients before surgery (24). Similarly, associations between cognitive impairment and gait disturbance have been presented by others (40).

If INPH is, in fact, associated with a dedifferentiation of functions, then treatment by CSF diversion should be expected to revert this development and lead to a functional redifferentiation. We found that several normally disparate functions improved after surgery (*Table 3*), and, as expected, there was some degree of redifferentiation of function (*Table 5*). However, because of the incomplete restoration, the postsurgery correlational pattern is still far from that of HIs.

Evaluation of Putative Predictors of Treatment Effect

INPH patients with vascular comorbidity, as suggested by the presence of hypertension, cardiovascular disease, and/or diabetes, performed significantly worse at baseline than patients without such ailments. The influence of vascular risk factors in INPH has been discussed by others (9, 20, 32), and a reduced effect of shunt treatment in INPH patients with cerebrovascular disease has been reported (7, 49). As mentioned earlier, we found no evidence that vascular comorbidity negatively affects the magnitude of improvement in neuropsychological functioning. Instead, it continues to contribute to the deficits remaining postoperatively. Stated differently, patients with vascular risk factors show the same degree of improvement as patients without vascular comorbidity, but they have significantly poorer results on most of the neuropsychological tests 3 months after shunt surgery (data not shown).

Similarly, we did not find any significant effect of onset symptom or sex on neuropsychological improvement after shunt treatment. Women outperformed men on the Rey auditory variables, both before and after surgery. Regarding onset symptom, no baseline differences in neuropsychological function were found between patients reporting gait disturbance versus cognitive deterioration as the primary onset symptom (24), and the magnitude of improvement was similar in the two groups; hence, no significant differences were found in neuropsychological performance after surgery. In previous studies, dementia preceding gait disturbance in the course of INPH has been shown to predict a poor response to shunt treatment (8, 19, 21). These studies lack explicit criteria for dementia, which makes comparisons uncertain. Patients reporting cognitive deterioration as their first symptom in our sample described memory problems and/or concentration difficulties; i.e., they did experience cognitive problems but were not demented before the onset of gait symptoms. None of the quantitative background variables of age, education, or disease duration were found to be of any practical use in predicting neuropsychological effects of shunt surgery in INPH.

Sample Representation and Study Design

All adults in the western part of Sweden who are diagnosed with chronic hydrocephalus are referred to our unit for evaluation and treatment. The diagnostic criteria used here are in agreement with the evidence-based clinical criteria recently presented by Relkin et al. (46), with two exceptions. First, we set no requirements regarding assessment of the nature and severity of cognitive impairment, apart from the routine neurological examination and an interview with relatives. Secondly, we chose to include all adult patients—regardless of age—on the basis of clinical findings. Although the use of an arbitrary age limit may enhance the diagnostic certainty in a studied sample, it may exclude patients who would benefit from shunt treatment. In the present sample, two patients were less than 40 years of age and thus younger than recommended in the guidelines (46). However, both of them showed clinically significant improvement regarding gait, dexterity, and neuropsychological performance after surgery.

We think that the patients included in this study are representative of patients with INPH. It is unfortunate that we were forced to exclude nine patients owing to a lack of evaluated effects of shunt revisions or valve adjustments. The advent of adjustable valves and the development of increasingly practical adjustment devices have made it possible to optimize treatment response by changing valve settings. When repeated adjustments were required (or when patients had multiple complications), it was not logistically possible to organize complete reevaluations in accordance with the study protocol. However, since many patients experience significant improvement only after more than one adjustment, we have recently initiated a double-blind study to evaluate the effects of repeated adjustments and to try to predict the optimal settings on the basis of early examinations.

Three aspects of our study design need to be discussed. First, patients may continue to improve well beyond 3 months after surgery, suggesting the existence of less dramatic and more slowly evolving effects than the rapid metabolic changes discussed earlier. This is supported by recently reported findings of an increased proportion of symptomatically improved patients from 33% at 3 months to 60% at 6 months (39). Hence, in some instances, our evaluations of the magnitude of neuropsychological change may underestimate the effect of shunt treatment as well as the proportion of improved patients.

Second, for the sake of comprehensibility, we chose to transform pre- and postoperative results, as well as changes after surgery, into percentages of normal performance (i.e., median values of HIs). Admittedly, estimates of the magnitude of change resulting from repeated exposure to the test procedures alone would be of great value, since it would make it possible to differentiate between the effects of training, chance, and treatment. We have initiated studies of the effects of repeated neuropsychological assessments (3 mo apart) on performance in healthy volunteers, but data are not yet available.

Third, this study is concerned with the statistical ascertainment of beneficial neuropsychological changes owing to shunt treatment. It does not, however, show the practical consequences of these changes, i.e., the effect on the quality of life or day-to-day-functioning of our patients. In an ongoing study, we have included ratings of activities of daily living and quality of life by raters who are blind to other investigations, including the neuropsychological assessment, and we hope to be able to report the results in the near future.

CONCLUSIONS

In this prospective study of 47 INPH patients, we found significant improvements in the results of neuropsychological tests measuring target reaction, dexterity, learning and memory, working memory, and naming speed and response selection, as well as in clinical symptoms, after 3 months of shunt treatment. None of six candidate variables (age, education, disease duration, vascular comorbidity, sex, and onset symptom) predicted these neuropsychological changes. The strength of the associations between normally disparate functions was reduced after surgery, reflecting the significant, yet incomplete, recovery from multiregional pathological changes.

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COMMENTS

The experience reported by Hellström et al. confirms clearly that patients with idiopathic normal pressure hydrocephalus (INPH) can hope to experience a significant improvement of their neuropsychological deficit after shunting. In my current clinical practice I inform these patients and their families that there is a probability of cognitive improvement in about two of three patients. Hellström et al. reported an even higher rate of 80.8%. However, this improvement rate depends on the methodology used to consider when these observed changes are significant. Indeed, if a positive change of 1 standard deviation on 50% of the tests is considered, the improvement rate is then around 50%. So I think to announce a chance of cognitive improvement in two of three patients remains reasonable information to be given to our patients.

Another important point in this article is that cognitive deterioration as a primary onset symptom is associated with similar clinical improvement after shunting. Indeed, memory problems and attention difficulties are different from dementia and as primary onset symptoms do not predict a poor response to shunting.

I regret the absence of data regarding a 12-month follow-up. It would have been interesting to know what evolution at 12 months this encouraging 80% neuropsychological improvement could have.

Christian Raftopoulos
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Hellström et al. presented a well-controlled prospective cohort study evaluating the neurocognitive response to ventricular cerebrospinal fluid (CSF) shunting for INPH. Whereas gait disturbance has been reported to be the most shunt-responsive of the classic INPH triad, neuropsychological symptoms of INPH are frequently more refractory to CSF shunting. In the current study, Hellström et al. successfully demonstrated both statistical and clinically significant improvements in neuropsychological tests of target reaction time, manual dexterity, motor speed, verbal learning and memory, and naming speed, response selection, and inhibition 3 months after surgery. Only simple reaction time and digit span (short-term or working memory) failed to improve after CSF shunting.

The value of this study is the well-controlled, prospective study design, using a well-matched cohort of non-INPH patients. The results presented here are encouraging and demonstrate that with appropriate patient selection, neurocognitive improvement can be expected in the majority of INPH patients, despite the failure to return to normal. This study also demonstrated that cognitive improvement can be expected in INPH patients with more marked neuropsychological deficits. It should be highlighted, however, that six patients requiring valve pressure adjustments (probably for lack of a clinical response) were excluded. This exclusion probably falsely elevated the response rate reported here. However, even with inclusion of these six patients as neuropsychological treatment failures, improvement occurred in the majority of patients.

The most important factor affecting the efficacy of CSF shunting for INPH remains patient selection. The high incidence of improvement reported here by Hellström et al. is probably in part attributable to their rigorous selection criteria. This article is a worthwhile contribution to the INPH literature.

Matthew J. McGirt
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This is a report about the neuropsychological outcome of 47 consecutively treated patients with INPH. Patients were treated over an approximately 5-year period. Although I do not regularly insist on ancillary confirmative diagnostic tests such as cisternography, lumbar drainage, or more complex evaluations of resistance to absorption, I never planned to publish my case results. Here, a relatively small number of patients had only cisternography and no other tests, which may be a weakness in the minds of some readers. Perhaps more importantly, there is no information about evaluations of quality of life. Nonetheless, I think the article provides useful information for NEUROSURGERY readers.

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