Neurosurgical Review (2021) 44:3323–3334
https://doi.org/10.1007/s10143-021-01495-4

ORIGINAL ARTICLE

Intraventricular infusion test accuracy in predicting short- and long-term outcome of iNPH patients: a 10-year update of a three-decade experience at a single institution

Gianluca Trevisi[1] · Francesco Signorelli[2] · Chiara de Waure[3] · Vito Stifano[2] · Cosimo Sturdà[2] · Alessandro Rapisarda[2] · Angelo Pompucci[4] · Annunziato Mangiola[1,5] · Carmelo Anile[2]

Received: 8 October 2020 / Revised: 19 December 2020 / Accepted: 4 February 2021 / Published online: 15 February 2021

Abstract

Objective In a previous work, we found that an Intracranial Elastance Index (IEI) ≥0.3 at ventricular infusion test had a high accuracy in predicting shunt response at 6 and 12 months in idiopathic normal pressure hydrocephalus (iNPH). The aim of this study was to verify the accuracy of IEI to predict response to shunt at both short- and long-term follow-up.

Methods Retrospective evaluation of 64 patients undergoing ventriculo-peritoneal shunting for iNPH between 2006 and 2015 based on a positive ventricular infusion test (IEI≥0.3). Patients were classified according to Krauss scale and mRS preoperatively, at 1-year and at last follow-up. An improvement of at least one point at Krauss score or at mRS was considered as a good outcome; unchanged or worsened patients were grouped as poor outcome.

Results Mean follow-up was 6.6 years. Improvement at Krauss scale was seen in 62.5% and 64.3% of patients at 1-year and last follow-up, respectively. Patients in good functional status (mRS≤2) increased from 25 in the preoperative period to 57% at both 1-year and last follow-up. IEI was significantly associated with Krauss (p=0.041) and mRS (p=0.036) outcome at last follow-up. Patients with worse preoperative Krauss and mRS had higher chance to improve but higher overall scores after treatment. At ROC curves, IEI showed a good long-term prediction of change in mRS from first year to last follow-up.

Conclusions IEI≥0.3 predicts outcomes at both short- and long-term, with more than 50% of patients being able to look after themselves after 6 years from treatment.

Keywords CSF outflow resistance · Infusion test · Intracranial Elastance Index · Outcome · Normal pressure hydrocephalus · Ventriculo-peritoneal shunting

Introduction

Idiopathic normal pressure hydrocephalus (iNPH) is considered a curable form of dementia characterized by the association of gait disturbances, cognitive impairment, and urinary incontinence and by radiographically evident ventriculomegaly. Ventricular shunting using programmable valves is the current standard of care for iNPH patients, with peritoneum or right heart atrium the most common shunting sites [30]. However, despite several non-invasive and invasive diagnostic tools are commonly used in preoperative workup, the selection of patients that will benefit from shunting is still the main clinical challenge in this syndrome [1, 13, 15, 32, 37].

Among invasive tests to predict shunt response, Katzman's infusion test evaluates CSF hydrodynamics [16, 22]: the measurement of CSF outflow resistance (R-out) is generally regarded as the most significant parameter to predict improvement after shunt placement [3, 4, 20]; however, a prospective European multicenter study concluded that R-out should not be used as a parameter to exclude patients from treatment [37].

✉ Gianluca Trevisi
trevisi.gianluca@gmail.com

[1] Neurosurgical Unit, Ospedale Spirito Santo, Pescara, Italy

[2] Institute of Neurosurgery, Fondazione Policlinico Universitario A. Gemelli IRCCS, Catholic University, Rome, Italy

[3] Department of Experimental Medicine, University of Perugia, Perugia, Italy

[4] Neurosurgical Unit, Ospedale Santa Maria Goretti, Latina, Italy

[5] Department of Neurosciences, Imaging and Clinical Sciences, "G. D'Annunzio" University, Chieti, Italy

In 2010 our group summarized almost 30 years of experience (1977–2005) in the treatment of iNPH showing that an Intracranial Elastance Index (IEI) above 0.3 was a robust predictor of positive response after shunting [2]. This index was automatically computed by a dedicated software developed at our institution by measuring the slope of the linear regression between the diastolic intracranial pressure (ICP) values and the corresponding amplitude of each CSF pulse pressure wave during an intraventricular infusion test. The test was considered as reliable if the coefficient of determination (R^2) was >0.8. All the patients who were selected for shunting using a threshold of IEI≥0.3 had a clinical improvement at 6- and 12-month follow-up indeed. On the other hand, patients with IEI<0.3 did not improve at the same time point follow-up. In the same series, R-out values did not correlate with clinical outcome, and reduction in ventricular size was not associated to clinical improvement, as it was found in only about 40% of improved cases.

On the basis of the above findings, starting from 2006, we systematically used intraventricular infusion test with IEI≥0.3 to select for shunting patients who presented with clinical and radiological stigmata of iNPH.

The aim of this paper is to verify the accuracy of IEI in predicting response to shunt at both short- and long-term follow-up in patients with suspected iNPH and at least 3 years of follow-up.

Methods

We reviewed clinical data of 64 consecutive patients who underwent ventricular shunting for iNPH between January 1, 2006, and December 31, 2015, based on a positive ventricular infusion test, namely, a test that showed an IEI≥0.3 and an R^2>0.8. The method used for the ventricular infusion test has been previously described [2]. All patients gave written informed consent for the analysis of clinical data.

Patients with secondary NPH (e.g., post-traumatic, post-hemorrhagic, post-infective, etc.) or evidence of long-standing overt ventriculomegaly (LOVA) were excluded as, due to different onset mechanisms [26], different parameters or thresholds could be appropriate for this subset of patients.

All iNPH patients were selected for the ventricular infusion test according to clinical evidence of partial or complete gait/urinary/cognitive clinical triad and evidence of ventriculomegaly with increased Evan's ratio, disproportionally effaced superior frontal sulci with respect to other sulci and Sylvian fissures, and reduced callosal angle at brain high-field MRI (≥1.5 T). All the patients also underwent pre-admission neuropsychological testing by dedicated and experienced neurologists and neuropsychologists. Patients who did not fulfill the above clinical, radiological, and neuropsychological selection criteria were excluded from the intraventricular infusion test. Patients who showed an IEI<0.3 were excluded from shunting and followed-up clinically and radiologically.

All the patients selected for surgery had a ventriculoperitoneal shunt using a Codman® Hakim® programmable valve. The proximal catheter was placed in the frontal horn of the right lateral ventricle in all cases. Valve initial opening pressure was set mainly according to infusion test opening pressure and adjusted by patients' anthropometric characteristics as height and abdominal circumference.

Data collection

All the ventricular infusion tests were reviewed, and the following parameters were collected: preoperative duration of symptoms, opening pressure, closing pressure, IEI, R-out, and ICP wave morphology before infusion and at the end of infusion according to the 4 class classifications based on changes in the relations of the three ICP peaks (percussion, tidal, and dicrotic peak) previously reported by our group [31].

Valve opening pressure and pressure modifications, shunt revisions/shunting site modifications, and surgical complications were recorded.

Clinical data were collected at 3 time points: preoperative period, at 12-month follow-up and at last follow-up, which occurred either in our outpatient clinic or via telephonic interview with patient/caregiver in January 2019. Clinical data were classified using the Krauss scale [24] and the modified Rankin scale (mRS): patients with mRS≤2 are generally considered to have a good level of function [10].

Patients were classified at 12 months and at last follow-up in three categories according to each of the above evaluation scales: improved, if there was an improvement of at least one point at total Krauss score or at mRS scale; unchanged, namely, no changes at total Krauss or mRS score; and worsened, decrease of at least one point at total Krauss or mRS score.

Results at last follow-up were compared both with preoperative status and with patients' status at 1 year. Improvement was considered as a good outcome, while stable or worsened patients were grouped as poor outcome (not improved).

Functional status was regarded as good if mRS≤2 and poor if mRS>2.

Statistical analysis

Mean Krauss score and mRS at 1-year and last follow-up were compared with preoperative values using a paired samples Student's *t* test.

Receiver operating characteristic (ROC) curves were used to determine IEI and R-out diagnostic accuracy in predicting shunt response at both 1-year follow-up and last follow-up.

Sensitivity, specificity, positive likelihood ratio (LR+), and negative likelihood ratio (LR−) of initial waveform characteristics to predict clinical outcomes response were calculated.

Independent samples Student's *t* test and Chi-squared test were used to analyze the differences of age, gender, length of symptoms (in months and dichotomized as ≤ 12/>12 months), IEI, R-out, and preoperative/1-year clinical status according to Krauss scale and mRS (the latter both as continuous value and dichotomized as ≤2/>2), between patients who were improved and not improved at Krauss and mRS at 1 year, last follow-up, and between last follow-up and 1 year. If the equal variance assumption was violated, a Welch test instead of a Student's test was used. Independent samples Student's *t* test was also used to assess possible differences in IEI, R-out, and preoperative clinical status between patients with different length of symptoms (≤12/>12 months).

Multivariate binomial logistic regression was also used to analyze the association between outcomes at both Krauss and mRS (improved/not improved) and length of symptoms, age, IEI, R-out, preoperative Krauss and mRS, and gender at 1 year, last follow-up, and between last follow-up and 1 year. Multivariate linear regression was used to determine the association between the same covariates and the total score at Krauss and mRS at 1-year and last follow-up.

Significance level was set at 0.05. Statistical analysis was performed using IBM SPSS Statistics V22.0.

Results

Study population

Sixty-four patients were analyzed. Demographics are reported in Table 1. All the patients had a minimum follow-up of 3 years (mean 6.6±2.5). One patient (1.5%) had a bleeding related to the intraventricular infusion test without any neurological sequelae. Twelve patients (18.7%) underwent revision surgery: 8 patients for abdominal catheter repositioning; 3 patients with previous history of abdominal surgeries had a conversion to ventriculo-atrial shunt since a poor peritoneal absorption was suspected; 2 patients (3%) developed a chronic subdural hematoma, one treated by transitory increasing of valve opening pressure up to the maximum setting level (20 cmH_2O) and the other requiring surgical evacuation and temporary shunt ligation. Twenty patients (31.3%) had a reduction of the valve opening pressure during follow-up in order to try to improve clinical benefit.

Clinical outcomes at 1 year

All the patients were alive at 1 year: 40 (62.5%) and 31 (48.4%) had a good outcome (improved) at Krauss scale and at mRS, respectively. Among patients with poor outcome (not improved) at Krauss score, 23 (36%) had an unchanged score, and one (1.5%) complained worsening of symptoms. All the 33 patients (51.6%) who had a poor outcome at mRS had an unchanged level of function, namely, none had a worse score at mRS.

Clinical outcomes at last follow-up

Overall, mean scores of Kraus scale both as total score and as score per domain, and of mRS, were all significantly reduced at both 1-year and last follow-up with the exception of cognition at Krauss at long term (Table 2).

Comparing the last follow-up with the follow-up at 1 year, 17 (30.4%) and 12 (21.4%) patients had an improvement of their outcome according to Krauss scale and mRS, respectively.

Outcome predictors analysis

Neither R-out nor IEI were shown to be accurate in predicting the outcome as the area under the curves (AUC) were all under 0.70 with the exception of elastance with respect to the change in mRS from first year to last follow-up (AUC 0.784; 95% CI 0.624–0.943). Also the waveform morphology was not proved accurate as LR+ and LR− were below 5 and above 0.2. Based on these results, waveform was not included in univariate and multivariate analysis.

A significant difference in both neurological and functional preoperative status was seen between patients who improved after shunting compared to patients who did not improve, at both 1-year follow-up and last follow-up. In particular, improved patients had worse preoperative Krauss and mRS than unimproved ones. However, after treatment, improved patients showed significant worse scores at both scales than not improved patients. Also R-out and IEI showed some significant differences between the two outcome groups (Tables 3 and 4).

Patients with length of symptoms >12 months showed significant lower values of R-out compared with patients treated at shorter onset of symptoms (mean 13.3 vs. 17.8, p=0.016). No differences of mean IEI, Krauss, and mRS were seen between patients with length of symptoms ≤/>12 months.

Regression analysis showed an association between preoperative clinical status and post-operative outcomes, with a significant association also between IEI and last follow-up outcomes at both Krauss and mRS (Tables 5 and 6). At last follow-up, an association between IEI and mRS and between R-out and Krauss score was also found (Table 6).

Results are summarized in Tables 2, 3, 4, 5, and 6 and Figs. 1 and 2.

Table 1 Demographics

Patients	Total	64
Gender	Male	41 (64%)
Age	Mean (SD)	73.2 (6.6) years
	Range	59–86 years
Length of symptoms	Mean (SD)	26.5 (20.3) months
	Range	1–96 months
	≤ 12 months	22 patients (34.4%)
	> 12 months	39 patients (60.9%)
	Not available	3 patients (4.7%)
Intracranial Elastance Index	Mean (SD)	0.597 (0.235)
	Range	0.320–1.630
R-out	Mean (SD)	15.204 (7.254)
	Range	1.780 - 38.680
Initial waveform morphology	Type I	6 (9.4%)
	Type II	19 (29.7%)
	Type III	29 (45.3%)
	Type IV	10 (15.6%)
Final waveform morphology	Type I	1 (1.6%)
	Type II	0
	Type III	9 (14%)
	Type IV	54 (84.4%)
Complications from infusion test	1 (1.5%) patient: bleeding	
Starting valve opening pressure	Mean	16 cmH2O
Complications after shunting	2 (3%) patients: chronic subdural hematoma	
	1 of them requiring surgical evacuation	
Valve pressure variations during follow-up	N° Patients	20 (31.3%)
Shunt revision surgery	Total	12 (18.7%) patients
	Conversion to ventriculo-atrial shunt	3 (4.7%) patients
Length of follow-up	Mean (SD)	6.6 (2.5) years
Death during follow-up	Total	8 (12.5%) patients
	Vascular accident	6 patients
	Pneumonia	1 patient
	Metastatic melanoma	1 patient

Discussion

iNPH is currently the only form of dementia that can be treated by surgery, with high chance of neurological improvement after a correct diagnosis, which is clinical and radiological. However, since the literature reported percentage of shunt non-responders ranges between 20 and 40% of patients [11], some ancillary, invasive tests have been developed to help clinicians to select patients that are more likely to improve after surgical treatment [19, 22, 32].

Among ancillary tests, two different categories of tests are described: subtraction tests, namely, tap test or prolonged lumbar drainage, and infusion tests, either lumbar or ventricular. Several studies have previously addressed the question of the predictive role of these invasive tests as standalone procedure or in combination: while specificity and positive predictive value are elevated, low sensitivity and negative predictive value are generally reported [4, 7–9, 20, 32, 37]. Briefly, in 2015 the American Academy of Neurology (AAN) guidelines summarized the literature evidences of the percentage of iNPH patients improving with shunting according to the results of ancillary tests [13]: 96% of patients with a positive tap test improved after treatment, as well as 94% of patients with a positive external lumbar drain test and 52% of patients with increased Rout at lumbar infusion test. However, a clinical improvement after shunting was

Table 2 Descriptive results

	Preoperative	1-year follow-up	*p*	Last follow-up (mean 6.6 ± 2.5 years)	*p*
Number of patients	64	64		56[#]	
Modified Rankin Scale					
Mean (SD)	3 (1)	2.4 (0.9)	<.001*	2.4 (1.2)	<.001*
0	0	0		1 (1.8%)	
1	7 (10.9%)	12 (18.8%)		15 (26.8%)	
2	9 (14.1%)	25 (39.1%)		16 (28.6%)	
3	22 (34.4%)	20 (31.3%)		10 (17.9%)	
4	25 (39%)	6 (9.4%)		13 (23.2%)	
5	1 (1.6%)	1 (1.6%)		1 (1.8%)	
Krauss Scale—Total					
Mean (SD)	4.9 (1.7)	3.6 (1.7)	<.001*	3.8 (2.1)	<.001*
0	0	1 (1.6%)		2 (3.6%)	
1	1 (1.6%)	3 (4.7%)		0	
2	5 (7.8%)	15 (23.4%)		16 (28.6%)	
3	8 (12.5%)	15 (23.4%)		14 (25%)	
4	13 (20.3%)	13 (20.3%)		7 (12.5%)	
5	13 (20.3%)	8 (12.5%)		5 (8.9%)	
6	12 (18.7%)	6 (9.4%)		6 (10.7%)	
7	7 (10.9%)	2 (3.1%)		1 (1.8%)	
8	4 (6.3%)	1 (1.6%)		2 (3.6%)	
9	1 (1.6%)	0		3 (5.4%)	
Krauss Scale—Gait					
Mean (SD)	1.9 (0.7)	1.3 (0.7)	<.001*	1.4 (0.9)	<.001*
0	2 (3.2%)	8 (12.5%)		9 (16.1%)	
1	11 (17.2%)	34 (53.1%)		22 (39.3%)	
2	41 (64%)	20 (31.3%)		19 (33.9%)	
3	10 (15.6%)	2 (3.1%)		6 (10.7%)	
Krauss Scale—Cognition					
Mean (SD)	1.4 (0.8)	1.1 (0.7)	<.001*	1.2 (0.8)	0.1
0	8 (12.5%)	10 (15.6%)		9 (16.1%)	
1	25 (39.1%)	36 (56.3%)		32 (39.3%)	
2	26 (40.6%)	18 (28.1%)		10 (33.9%)	
3	5 (7.8%)	0		5 (10.7%)	
Krauss Scale—Urinary					
Mean (SD)	1.5 (1)	1.2 (0.9)	<.001*	1.2 (1)	0.007*
0	9 (14.1%)	13 (20.3%)		14 (25%)	
1	24 (37.5%)	33 (51.6%)		23 (41.1%)	
2	18 (28.1%)	11 (17.2%)		12 (21.4%)	
3	13 (20.3%)	7 (10.9%)		7 (12.5%)	

*Significant at paired samples Student's *t* test (paired with preoperative mean value)

#Eight patients had died for causes not related to the shunt nor to the hydrocephalus during follow-up. See manuscript text for detail

seen in 71% of patients with a negative tap test, in 33% of patients with a negative external lumbar drain test, and in 69% of patients with no increased Rout at lumbar infusion test.

Historically our group preferred ventricular to lumbar infusion test as in the past decades a prolonged overnight ICP monitoring was performed through the same access. Intraventricular infusion test was also deemed as more reliable than lumbar infusion test [6] and allowed a deeper insight of pathophysiology of iNPH [2]. Summarizing a clinical experience of 3 decades, an IEI≥0.3 at ventricular infusion test was

Table 3 Independent samples *t* test

1-year follow-up						
	Krauss			mRS		
	Improved (*n*=40)	Not improved (*n*=24)		Improved (*n*=31)	Not improved (*n*=33)	
	Mean (SD)	Mean (SD)	*p*	Mean (SD)	Mean (SD)	*p*
Length of symptoms (months)	27 (19.7)	25.6 (21.7)	0.794	26 (19.4)	26.9 (21.4)	0.859
Age at treatment (years)	74 (6.5)	71.8 (6.7)	0.189	74.6 (6.4)	71.8 (6.6)	0.091
Intracranial Elastance Index	0.59 (0.2)	0.6 (0.3)	0.935	0.57 (0.2)	0.62 (0.3)	0.346#
R-out	15.9 (7.8)	14.1 (6.1)	0.353	17.3 (8)	13.3 (6)	0.027*
Preoperative mRS	3.3 (0.9)	2.7 (1.2)	0.015*	3.5 (0.6)	2.6 (1.1)	< .001*#
Preoperative Krauss—Total	5.5 (1.6)	4.0 (1.6)	0.001*	5.6 (1.5)	4.3 (1.8)	0.002*
mRS at 1 year	2.2 (0.8)	2.6 (1.2)	0.192#	2.1 (0.7)	2.6 (1.1)	0.029*#
Krauss—Total at 1 year	3.2 (1.5)	4.1 (1.8)	0.034*	3.3 (1.3)	3.8 (1.9)	0.258#
Last follow-up—compared to preoperative status						
	Krauss			mRS		
	Improved (*n*=36)	Not improved (*n*=20)		Improved (*n*=31)	Not improved (*n*=25)	
	Mean (SD)	Mean (SD)	*p*	Mean (SD)	Mean (SD)	*p*
Length of symptoms (months)	25 (17.6)	26 (21.8)	0.851	21.6 (14.7)	29.6 (22.6)	0.131
Age at treatment (years)	72.9 (6.7)	74.4 (6.7)	0.420	72.8 (6.9)	74.2 (6.4)	0.465
Intracranial Elastance Index	0.5 (0.2)	0.7 (0.2)	0.069#	0.5 (0.2)	0.6 (0.2)	0.038*
R-out	17.1 (7.8)	12.3 (4.9)	0.006*#	17.3 (6.9)	13.0 (7.1)	0.027*
Preoperative mRS	3.1 (1)	2.9 (1)	0.317	3.4 (0.8)	2.6 (1.2)	0.006*#
Preoperative Krauss—Total	5.3 (1.6)	4.3 (1.9)	0.046*	5.1 (1.4)	4.7 (2.1)	0.371#
mRS at 1-year follow-up	2.2 (1)	2.5 (0.9)	0.396	2.3 (0.9)	2.3 (1)	0.909
Krauss—Total at 1 year	3.6 (1.8)	3.4 (1.5)	0.538	3.6 (1.7)	3.4 (1.6)	0.588
mRS at last follow-up	2 (1)	3.1 (1.2)	< .001*	1.9 (0.8)	3 (1.3)	< .001*#
Krauss—Total at last follow-up	2.9 (1.4)	5.5 (2.3)	< .001*#	3 (1.4)	4.8 (2.5)	0.004*#
Last follow-up - compared to 1-year follow-up						
	Krauss			mRS		
	Improved (*n*=17)	Not improved (*n*=39)		Improved (*n*=12)	Not improved (*n*=44)	
	Mean (SD)	Mean (SD)	*p*	Mean (SD)	Mean (SD)	*p*
Length of symptoms (months)	22.3 (19.6)	26.7 (19)	0.450	17.7 (15.1)	27.4 (19.7)	0.137
Age at treatment (years)	71.5 (6.3)	74.3 (6.7)	0.160	71.3 (7.2)	74 (6.5)	0.221
Intracranial Elastance Index	0.6 (0.2)	0.6 (0.2)	0.533	0.5 (0.2)	0.6 (0.2)	0.059
R-out	16.9 (8.3)	14.7 (6.8)	0.294	14.3 (5.2)	15.7 (7.7)	0.584
Preoperative mRS	3.1 (1)	3 (1)	0.913	3.2 (0.9)	3 (1.1)	0.622
Preoperative Krauss—Total	5.5 (1.5)	4.7 (1.8)	0.131	5.1 (1.6)	4.9 (1.8)	0.736
mRS at 1-year follow-up	2.6 (1.1)	2.2 (0.8)	0.074	2.8 (1)	2.2 (0.9)	0.028*
Krauss—Total at 1 year	4.9 (1.5)	2.9 (1.4)	< .001*	4.8 (1.7)	3.2 (1.5)	0.003*
mRS at last follow-up	1.8 (1.1)	2.6 (1.2)	0.019*	1.5 (0.9)	2.6 (1.2)	0.003*
Krauss—Total at last follow-up	2.8 (1.6)	4.3 (2.2)	0.015*	2.5 (1.4)	4.2 (2.2)	0.016*

Student's *t* test (please refer to # for exceptions)

*Significant

#Welch's unequal variances *t* test has been applied instead of Student's *t* test as Levene's test was significant ($p < .05$), suggesting a violation of the equal variance assumption

Table 4 Chi-squared test

1-year follow-up						
	Krauss			mRS		
	Improved (*n*=40)	Not improved (*n*=24)		Improved (*n*=31)	Not improved (*n*=33)	
	Frequency (%)	Frequency (%)	*p*	Frequency (%)	Frequency (%)	*p*
Male gender	28 (43.8)	13 (30.3)	0.2	20 (31.3)	21 (33)	0.9
Length of symptoms ≤ 12 months#	12 (19.7)	10 (16.4)	0.3	11 (18)	11 (18)	0.8
Preoperative mRS ≤ 2	6 (9.4)	10 (15.6)	0.017*	2 (3.1)	14 (21.9)	<.001*
Last follow-up—compared to preoperative status						
	Krauss			mRS		
	Improved (*n*=36)	Not improved (*n*=20)		Improved (*n*=31)	Not improved (*n*=25)	
	Frequency (%)	Frequency (%)	*p*	Frequency (%)	Frequency (%)	*p*
Male gender	24 (42.9)	11 (19.6)	0.4	20 (35.7)	15 (26.8)	0.7
Length of symptoms ≤ 12 months#	12 (22.6)	8 (15)	0.8	12 (22.6)	8 (15)	0.4
Preoperative mRS ≤ 2	9 (16)	6 (10)	0.7	4 (7.1)	11 (19.6)	0.009*
mRS ≤ 2 at 1 year	26 (46.4)	9 (16)	0.044*	22 (39.2)	12 (23.2)	0.1
Last follow-up—compared to 1-year follow-up						
	Krauss			mRS		
	Improved (*n*=17)	Not improved (*n*=39)		Improved (*n*=12)	Not improved (*n*=44)	
	Frequency (%)	Frequency (%)	*p*	Frequency (%)	Frequency (%)	*p*
Male gender	11 (19.6)	24 (42.9)	0.8	8 (14.3)	27 (48.2)	0.7
Length of symptoms ≤ 12 months#	8 (15)	12 (22.6)	0.2	6 (11.3)	14 (26.4)	0.2
Preoperative mRS ≤ 2	5 (8.9)	10 (17.8)	0.8	3 (5.3)	12 (21.4)	0.9
mRS ≤ 2 at 1 year	9 (16)	26 (46.4)	0.3	6 (10.7)	29 (51.8)	0.3

*Significant

#Data on preoperative length of symptoms were available in 61 patients

Table 5 Binomial logistic regression: outcomes (improved or not improved) according to Krauss scale total score and mRS

Dependent variable	Covariates	Odds ratio	*p*	95% Confidence interval	
				Lower bound	Upper bound
Krauss Scale—Total					
Outcome at 1 year compared to preoperative status: Krauss (improved or not improved)	Length of symptoms (months)	1.008	0.656	0.975	1.042
	Age	0.933	0.184	0.843	1.034
	Intracranial Elastance Index	0.344	0.430	0.024	4.867
	R-out	1.020	0.693	0.925	1.124
	Preoperative mRS	0.811	0.604	0.368	1.789
	Preoperative Krauss—Total	0.561	0.033*	0.330	0.953
	Gender (M)	0.302	0.107	0.070	1.297
Outcome at last follow-up compared to preoperative status: Krauss (improved or not improved)	Length of symptoms (months)	1.011	0.478	0.982	1.040
	Age	1.020	0.678	0.928	1.121
	Intracranial Elastance Index	31.659	0.041*	1.152	869.724
	R-out	0.941	0.210	0.855	1.035
	Preoperative mRS	1.163	0.706	0.531	2.550
	Preoperative Krauss—Total	0.735	0.178	0.469	1.150
	Gender (M)	0.314	0.085	0.084	1.173
Outcome at last follow-up compared to 1-year follow-up: Krauss (improved or not improved)	Length of symptoms (months)	1.022	0.272	0.983	1.063
	Age	1.117	0.062	0.994	1.254
	Intracranial Elastance Index	1.209	0.909	0.047	31.375
	R-out	0.936	0.177	0.851	1.030
	Preoperative mRS	2.162	0.142	0.773	6.041
	Preoperative Krauss—Total	0.477	0.032*	0.242	0.939
	Gender (M)	1.277	0.747	0.290	5.625
Modified Rankin Scale (mRS)					
Outcome at 1 year compared to preoperative status: mRS (improved or not improved)	Length of symptoms (months)	0.016	0.704	0.976	1.037
	Age	0.050	0.183	0.849	1.032
	Intracranial Elastance Index	1.620	0.880	0.033	18.741
	R-out	0.050	0.114	0.838	1.019
	Preoperative mRS	0.498	0.022*	0.121	0.851
	Preoperative Krauss—Total	0.234	0.656	0.569	1.425
	Gender (M)	0.706	0.724	0.195	3.109
Outcome at last follow-up compared to preoperative status: mRS (improved or not improved)	Length of symptoms (months)	1.031	0.065	0.998	1.065
	Age	1.024	0.644	0.927	1.130
	Intracranial Elastance Index	41.943	0.036*	1.281	1373.241
	R-out	0.960	0.373	0.877	1.051
	Preoperative mRS	0.175	0.003*	0.055	0.557
	Preoperative Krauss—Total	1.667	0.060	0.979	2.839
	Gender (M)	0.161	0.023*	0.033	0.778
Outcome at last follow-up compared to 1-year follow-up: mRS (improved or not improved)	Length of symptoms (months)	1.060	0.064	0.997	1.127
	Age	1.053	0.348	0.945	1.172
	Intracranial Elastance Index	121.256	0.068	0.699	21041.584
	R-out	1.037	0.524	0.927	1.160
	Preoperative mRS	0.912	0.856	0.339	2.455
	Preoperative Krauss—Total	0.999	0.997	0.542	1.839
	Gender (M)	0.351	0.235	0.062	1.974

Not improved coded as class 1

*Significant

detected as highly accurate in prediction of shunt response, with a 100% positive response at 1 year. Moreover, patients with IEI<0.3 had no improvement at 1 year. This diagnostic accuracy outstood the predictive values reported for other ancillary tests.

Therefore, despite intraventricular infusion test is a more invasive diagnostic tool than spinal infusion or subtraction diagnostic tests, our results encouraged its use in our clinical practice.

However, present results at 1 year are less satisfactory than our previously published ones. A number of reasons could explain these differences. One could be an increased indication to shunt surgery based on the positive influence of our previous findings about IEI. Indeed, several conditions may mimic iNPH, with only about 30% of patients presenting with enlarged ventricles and suggestive clinical picture actually harboring iNPH [25]. Moreover, a beta-amyloid deposit and hyperphosphorylated tau have been reported in up to 60% of patients undergoing shunting for iNPH [19]. Worse post-operative outcomes, particularly in the cognitive domain, are reported in these patients [18]. The possible interweaving of iNPH, Alzheimer's disease, Parkinson's disease, Parkinsonisms, and Lewy body disease stresses the need of a multidisciplinary team to select iNPH patients to submit to neurosurgical treatment [15, 24, 25, 27, 33, 35]. However, all our patients underwent accurate neuroradiologic assessment and neuropsychological testing before neurosurgical management, and none of them received a diagnosis of other neurological conditions during post-operative follow-up. Indeed, while some studies on the association between tap test and amyloid deposits are available [27], a dedicated study to compare infusion test metrics between patients affected by standalone iNPH and by concomitant iNPH and neurodegenerative diseases is currently lacking.

Table 6 Linear regression: outcomes according to Krauss scale total score and mRS total value

Dependent variable	Covariates	Standardized coefficient	*p*	95% Confidence interval	
				Lower bound	Upper bound
Krauss at 1-year follow-up	Length of symptoms (months)	0.027	0.811	−0.016	0.021
	Age	−0.090	0.435	−0.081	0.035
	Intracranial Elastance Index	0.057	0.631	−1.252	2.048
	R-out	0.017	0.880	−0.049	0.057
	Preoperative mRS	0.116	0.453	−0.310	0.685
	Preoperative Krauss—Total	0.561	< .001*	0.234	0.799
	Gender (M)	−0.064	0.589	−1.036	0.594
mRS at 1-year follow-up	Length of symptoms (months)	0.064	0.546	−0.007	0.013
	Age	−0.144	0.180	−0.051	0.010
	Intracranial Elastance Index	0.015	0.891	−0.812	0.932
	R-out	−0.098	0.352	−0.041	0.015
	Preoperative mRS	0.678	< .001*	0.363	0.889
	Preoperative Krauss—Total	0.026	0.857	−0.136	0.163
	Gender (M)	−0.053	0.629	−0.535	0.326
Krauss at last follow-up	Length of symptoms (months)	−0.186	0.179	−0.053	0.010
	Age	0.185	0.160	−0.025	0.149
	Intracranial Elastance Index	0.245	0.070	−0.226	5.408
	R-out	−0.332	0.022*	−0.190	−0.016
	Preoperative mRS	0.046	0.797	−0.661	0.856
	Preoperative Krauss—Total	0.465	0.012*	0.131	1.004
	Gender (M)	0.129	0.369	−0.715	1.886
mRS at last follow-up	Length of symptoms (months)	0.087	0.500	−0.011	0.022
	Age	0.069	0.570	−0.033	0.059
	Intracranial Elastance Index	0.345	0.007*	0.581	3.551
	R-out	−0.249	0.062	−0.090	0.002
	Preoperative mRS	0.252	0.132	−0.095	0.704
	Preoperative Krauss—Total	0.329	0.053	−0.003	0.457
	Gender (M)	−0.162	0.228	−1.101	0.270

*Significant

Moreover, in the present study, shunt efficacy may have been reduced by an elevated initial valve opening pressure setting or by a lack of progressive adjustment of the optimal valve setting for individual patient in the context of an evolving disease. Some subtle shunt malfunctions may have also been missed. These have been recognized as frequent causes of long-term loss of efficacy of the treatment [12].

Nonetheless, this series shows that at long-term follow-up, outcome according to Krauss scale and mRS was good in 64.3% and 55.4% of cases, respectively. Maybe more relevant, there was an overall shift towards better levels of function as 57% of patients were in mRS≤2 at 1 year, compared to 25% in the preoperative period, and this percentage was maintained at last follow-up. Namely, the majority of patients were independent more than 6 years after treatment. This trend towards a long-term improvement is different to what has been recently reported by other groups, whose early results were better than long-term ones [19, 21, 28, 34].

The analysis of outcome predictors showed that IEI is associated with outcome, as it was significantly lower in patients who improved at mRS at last follow-up (Table 3), and showed a strong positive association (odds ratio>30) with outcomes at last follow-up at both Krauss and mRS, meaning that increasing IEI significantly increases the odds of poor outcome (Table 5, Fig. 1). Increasing IEI has also significant association with higher mRS at last follow-up (Table 6). On the other hand, we previously showed a lack of improvement in patients with IEI<0.3 [2]. This seems to suggest that both a low and an elevated IEI can predict a poor response to shunting. Further studies are needed to confirm these data and to try to identify also an upper threshold of IEI values for non-responders.

Moreover, patients who were in worse clinical status before shunting had a higher chance to improve their outcome at both 1-year and last follow-up (Tables 3, 4, 5, and 6). Indeed, 21 (44%) of the 48 patients who were operated upon with mRS>2 had an improvement to mRS≤ 2 at 1 year (p<.001; Table 4).

Lastly, our results confirm that R-out is not an accurate parameter to predict the shunt response. While R-out was initially regarded as the most sensitive parameter to predict surgical outcome [3–5, 20], more recently, it has been shown that this value could be influenced by length of pathology [7] and should not be used to preclude patients from treatment [37]. In agreement with data reported by Czosnyka et al. [7], duration of symptoms

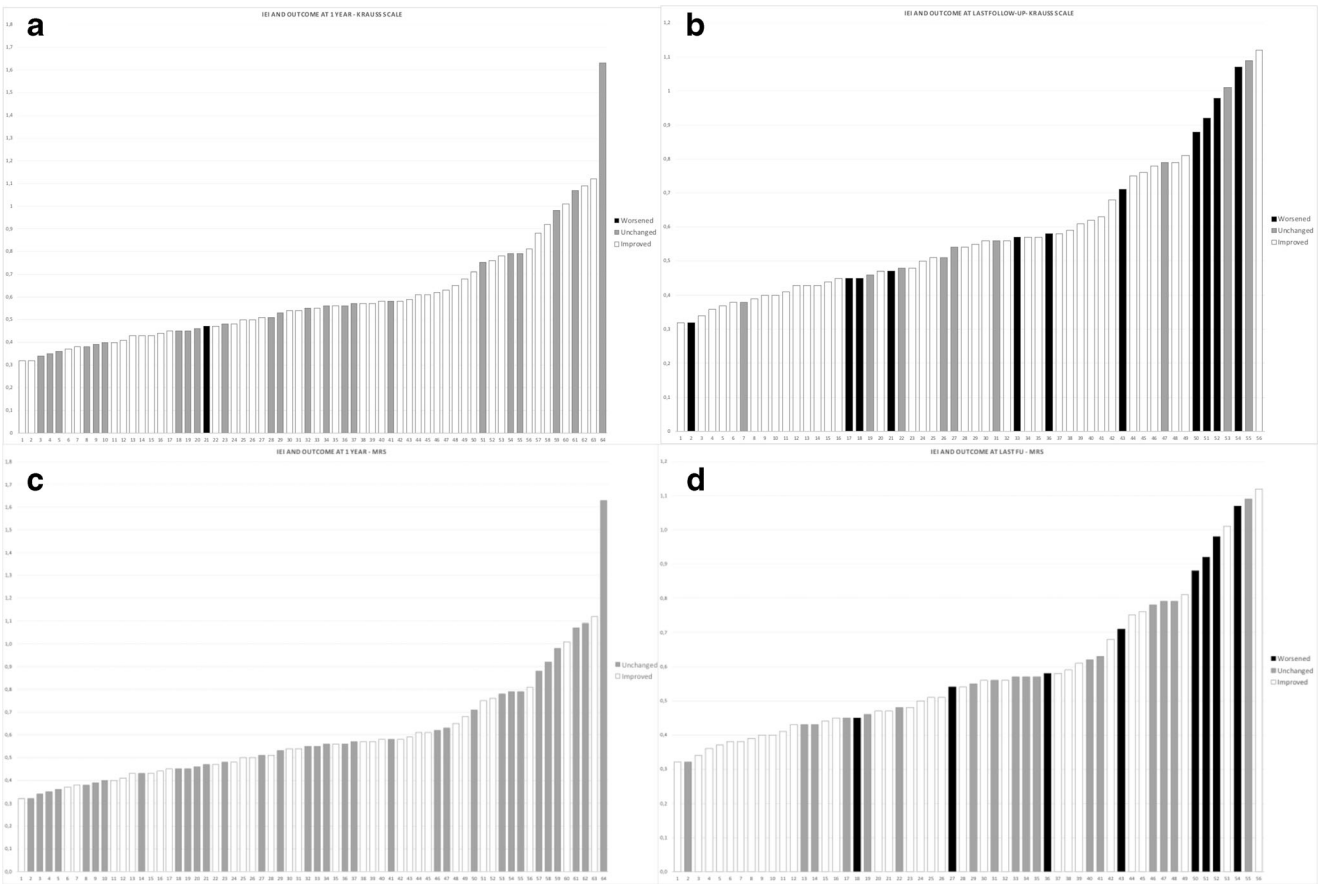

Fig. 1 Intracranial Elastance Index (IEI) and outcome at Krauss scale at 1-year (**a**) and last follow-up (**b**) and at mRS at 1-year (**c**) and last follow-up (**d**). White bars, improved; gray bars, unchanged; black bars, worsened. Outcomes are compared to preoperative status

longer than 1 year was associated to lower mean R-out in our series (p=0.01).

Despite the above considerations, our current results suggest that no single one CSF dynamics parameter tested by means of the intraventricular infusion test can be used as absolute predictor of shunt response.

Indeed, differently from our previous more encouraging experience, results from this series are in line with those reported by other groups using other one or more diagnostic tests such as tap test, extended lumbar drainage, or spinal infusion test and even to some studies where only clinical-radiological parameters were used to select patients for shunting [14, 17, 19, 23, 29, 32].

This may raise the legitimate doubt about the opportunity to perform a diagnostic test that is as invasive as the actual treatment in its cranial part. Regarding safety, in the same time period considered in this manuscript, a strict pre-selection of patients on the basis of clinical, neuropsychological, and neuroradiological allowed us to reduce to about 7% the number of patients with suspected iNPH that had a negative intraventricular infusion test (IEI<0.3) and were therefore not elected for shunting. None of these patients had complications from the ventriculostomy. Among the 64 patients with a positive test that underwent definitive shunting, only 1 (1.5%) had a complication (Table 1), namely, a bleeding with no neurological sequalae, related to ventriculostomy/ventricular infusion test, while no infections were recorded. This complication rate is in line with the intrinsic risk of the ventricular puncture needed for a shunting procedure. However, despite our experience confirms that the intraventricular infusion test is safe for patients and easy to be performed by a trained group of neurosurgeons using a dedicated computer software, its supposed superior predictive value over other ancillary tests is not confirmed by our results. Therefore, this invasive procedure should be subject to special consideration. It could indeed represent the last tier of a diagnostic algorithm that privileges alternative diagnostic methods, including the lumbar subtraction and/or infusion tests, and reserves the ventricular infusion test to those patients with a high suspicion of iNPH that could not be fully confirmed by previous less invasive tests.

Furthermore, lumbo-peritoneal shunting is emerging as a possible alternative in iNPH treatment, with similar outcomes but still higher failure rate compared to ventriculo-peritoneal

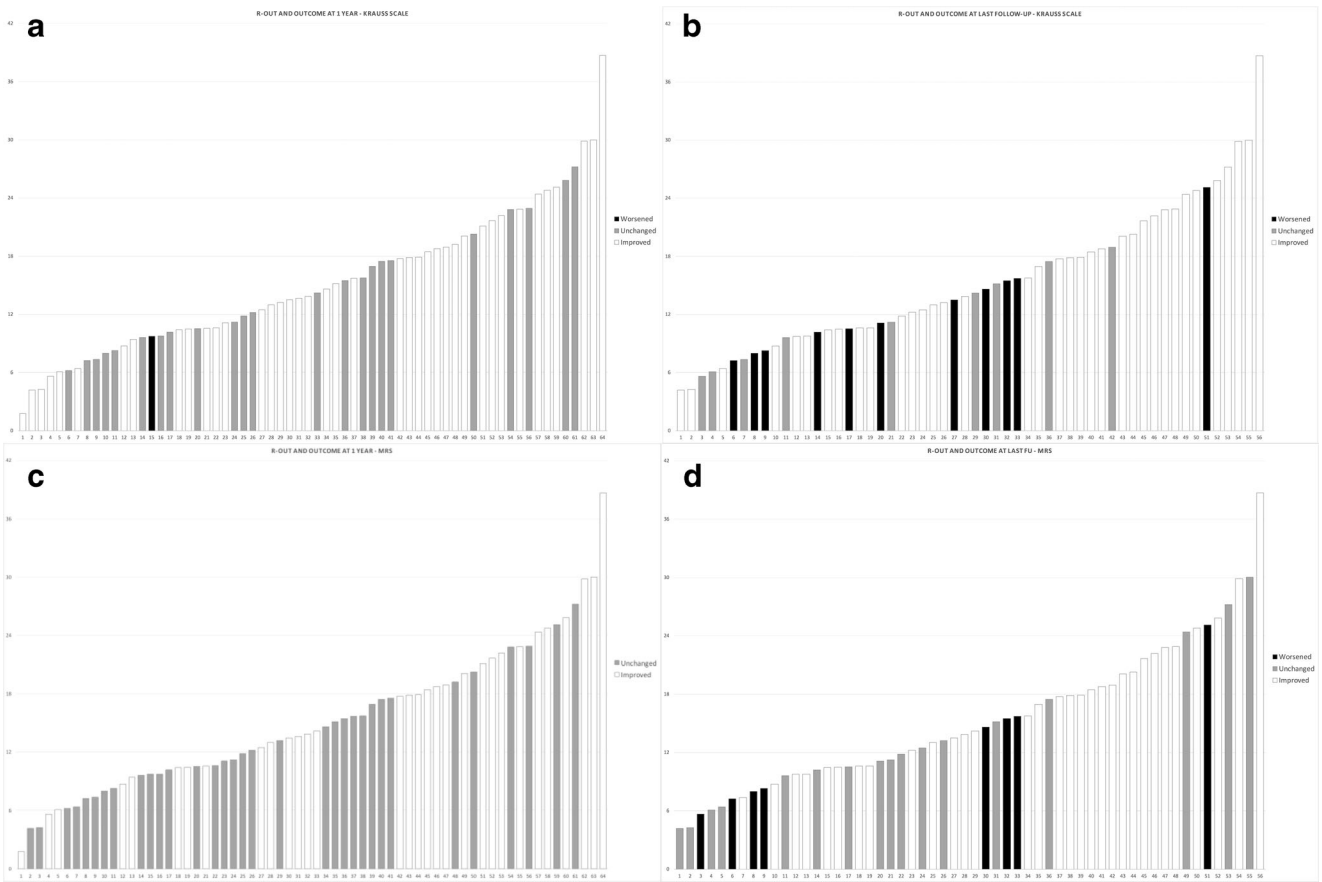

Fig. 2 CSF outflow resistance (R-out) and outcome at Krauss scale at 1-year (**a**) and last follow-up (**b**) and at mRS at 1-year (**c**) and last follow-up (**d**). White bars, improved; gray bars, unchanged; black bars, worsened. Outcomes are compared to preoperative status

shunting [23, 36]. Should lumbo-peritoneal shunting be recognized as the treatment of choice in iNPH in the next future, the role of intraventricular infusion test could be further diminished.

Study limitations

Main limitations of the present series are its retrospective nature, the limited number of cases, and the pre-selection of patients according to IEI. The latter prevented to calculate the negative predictive value of IEI. However, we previously showed that patients below 0.3 of IEI had no benefit from shunting at 6- and 12-month evaluation [2].

A prospective, multicentric, randomized trial could further support the role of IEI in the prediction of both short- and long-term outcomes after shunting and compare it to the diagnostic accuracy of other ancillary tests.

Conclusions

iNPH is a benign pathology that can severely limit the quality of life of patients, with up to 75% of patients living in a dependent functional status (mRS>2). Accurate selection of patients according to clinical, neuroradiological, and neuropsychological data is essential. Intraventricular infusion test is an invasive adjuvant method to select patients who will benefit from surgery. Preoperative status and IEI are significantly associated with last follow-up outcomes. Our past and present data show that a threshold of 0.3 of IEI can be helpful to predict the response to shunt at both short- and long-term follow-up. However, no single one CSF dynamics parameter analyzed in this series seems to outstand the predictive values of other ancillary tests. Further studies are needed to investigate whether also an upper threshold of IEI exists to predict poor response to shunting.

Authors' contribution Gianluca Trevisi: Conceptualization, data curation, investigation, methodology, roles/writing—original draft, and writing—review and editing
Francesco Signorelli: Data curation, investigation, methodology, roles/writing—original draft, and writing—review and editing
Chiara de Waure: Formal analysis, methodology, and writing—review and editing
Vito Stifano: Data curation and writing—review and editing
Cosimo Sturdà: Data curation and writing—review and editing
Alessandro Rapisarda: Data curation and writing—review and editing
Angelo Pompucci: Investigation, data curation, and writing—review and editing
Annunziato Mangiola: Supervision and writing—review and editing
Carmelo Anile: Supervision and writing—review and editing

Availability of data and material Not applicable.

Code availability Not applicable.

Declarations

Ethics approval Not applicable.

Consent to participate All the patients signed an informed consent for the treatment described in the manuscript.

Consent for publication All the patients signed an informed consent allowing use of their clinical data for publication in anonymous form.

Conflict of interest The authors declare no competing interests.

References

1. Andersson J, Rosell M, Kockum K, Söderström L, Laurell K (2017) Challenges in diagnosing normal pressure hydrocephalus: evaluation of the diagnostic guidelines. eNeurologicalSci 7:27–31. https://doi.org/10.1016/j.ensci.2017.04.002
2. Anile C, De Bonis P, Albanese A, Di Chirico A, Mangiola A, Petrella G, Santini P (2010) Selection of patients with idiopathic normal-pressure hydrocephalus for shunt placement: a single-institution experience. J Neurosurg 113:64–73. https://doi.org/10.3171/2010.1.JNS091296
3. Boon AJW, Tans JTJ, Delwel EJ, Egeler-Peerdeman SM, Hanlo PW, Wurzer HAL, Avezaat CJJ, de Jong DA, Gooskens RHJM, Hermans J (1997) Dutch normal-pressure hydrocephalus study: prediction of outcome after shunting by resistance to outflow of cerebrospinal fluid. J Neurosurg 87:687–693
4. Boon AJW, Tans JTJ, Delwel EJ, Egeler-Peerdeman SM, Hanlo PW, Wurzer HAL, Hermans J (2000) The Dutch normal-pressure hydrocephalus study. Surg Neurol 53:201–207. https://doi.org/10.1016/S0090-3019(00)00182-8
5. Børgesen SE, Gjerris F (1982) The predictive value of conductance to outflow of CSF in normal pressure hydrocephalus. Brain J Neurol 105:65–86. https://doi.org/10.1093/brain/105.1.65
6. Czosnyka M, Whitehouse H, Smielewski P, Simac S, Pickard JD (1996) Testing of cerebrospinal compensatory reserve in shunted and non-shunted patients: a guide to interpretation based on an observational study. J Neurol Neurosurg Psychiatry 60:549–558. https://doi.org/10.1136/jnnp.60.5.549
7. Czosnyka Z, Owler B, Keong N, Santarius T, Baledent O, Pickard JD, Czosnyka M (2011) Impact of duration of symptoms on CSF dynamics in idiopathic normal pressure hydrocephalus: duration of symptoms and CSF dynamics. Acta Neurol Scand 123:414–418. https://doi.org/10.1111/j.1600-0404.2010.01420.x
8. Eide PK (2016) The correlation between pulsatile intracranial pressure and indices of intracranial pressure-volume reserve capacity: results from ventricular infusion testing. J Neurosurg 125:1493–1503. https://doi.org/10.3171/2015.11.JNS151529
9. Eide PK, Sorteberg W (2016) Outcome of surgery for idiopathic normal pressure hydrocephalus: role of preoperative static and pulsatile intracranial pressure. World Neurosurg 86:186–193.e1. https://doi.org/10.1016/j.wneu.2015.09.067
10. Farrell B, Godwin J, Richards S, Warlow C (1991) The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. J Neurol Neurosurg Psychiatry 54:1044–1054
11. Giordan E, Palandri G, Lanzino G, Murad MH, Elder BD (2018) Outcomes and complications of different surgical treatments for idiopathic normal pressure hydrocephalus: a systematic review and meta-analysis. J Neurosurg 131:1–13. https://doi.org/10.3171/2018.5.JNS1875

12. Grasso G, Torregrossa F, Leone L, Frisella A, Landi A (2019) Long-term efficacy of shunt therapy in idiopathic normal pressure hydrocephalus. World Neurosurg 129:e458–e463. https://doi.org/10.1016/j.wneu.2019.05.183
13. Halperin JJ, Kurlan R, Schwalb JM, Cusimano MD (2015) Practice guideline: Idiopathic normal pressure hydrocephalus: response to shunting and predictors of response. 9
14. Hashimoto M, Ishikawa M, Mori E, Kuwana N, Study of INPH on neurological improvement (SINPHONI) (2010) Diagnosis of idiopathic normal pressure hydrocephalus is supported by MRI-based scheme: a prospective cohort study. Cerebrospinal Fluid Res 7:18. https://doi.org/10.1186/1743-8454-7-18
15. Hellström P, Klinge P, Tans J, Wikkelsø C (2012) The neuropsychology of iNPH: findings and evaluation of tests in the European multicentre study. Clin Neurol Neurosurg 114:130–134. https://doi.org/10.1016/j.clineuro.2011.09.014
16. Hussey F, Schanzer B, Katzman R (1970) A simple constant-infusion manometric test for measurement of CSF absorption. II Clinical studies. Neurology 20:665–680. https://doi.org/10.1212/wnl.20.7.665
17. Ishikawa M, Hashimoto M, Mori E, Kuwana N, Kazui H (2012) The value of the cerebrospinal fluid tap test for predicting shunt effectiveness in idiopathic normal pressure hydrocephalus. Fluids Barriers CNS 9:1. https://doi.org/10.1186/2045-8118-9-1
18. Jang H, Park SB, Kim Y, Kim KW, Lee JI, Kim ST, Lee KH, Kang E-S, Choe YS, Seo SW, Kim HJ, Kim YJ, Yoon CW, Na DL (2018) Prognostic value of amyloid PET scan in normal pressure hydrocephalus. J Neurol 265:63–73. https://doi.org/10.1007/s00415-017-8650-5
19. Junkkari A, Luikku AJ, Danner N, Jyrkkänen HK, Rauramaa T, Korhonen VE, Koivisto AM, Nerg O, Kojoukhova M, Huttunen TJ, Jääskeläinen JE, Leinonen V (2019) The Kuopio idiopathic normal pressure hydrocephalus protocol: initial outcome of 175 patients. Fluids Barriers CNS 16:21. https://doi.org/10.1186/s12987-019-0142-9
20. Kahlon B (2002) Comparison between the lumbar infusion and CSF tap tests to predict outcome after shunt surgery in suspected normal pressure hydrocephalus. J Neurol Neurosurg Psychiatry 73:721–726. https://doi.org/10.1136/jnnp.73.6.721
21. Kahlon B, Sjunnesson J, Rehncrona S (2007) Long-term outcome in patients with suspected normal pressure hydrocephalus. Neurosurgery 60:327–332. https://doi.org/10.1227/01.NEU.0000249273.41569.6E
22. Katzman R, Hussey F (1970) A simple constant-infusion manometric test for measurement of CSF absorption. I. Rationale and method. Neurology 20:534–544. https://doi.org/10.1212/wnl.20.6.534
23. Kazui H, Miyajima M, Mori E, Ishikawa M, SINPHONI-2 Investigators (2015) Lumboperitoneal shunt surgery for idiopathic normal pressure hydrocephalus (SINPHONI-2): an open-label randomised trial. Lancet Neurol 14:585–594. https://doi.org/10.1016/S1474-4422(15)00046-0
24. Krauss JK, Droste DW, Vach W, Regel JP, Orszagh M, Borremans JJ, Tietz A, Seeger W (1996) Cerebrospinal fluid shunting in idiopathic normal-pressure hydrocephalus of the elderly: effect of periventricular and deep white matter lesions. Neurosurgery 39:292–299; discussion 299-300. https://doi.org/10.1097/00006123-199608000-00011
25. Macki M, Mahajan A, Shatz R, Air EL, Novikova M, Fakih M, Elmenini J, Kaur M, Bouchard KR, Funk BA, Schwalb JM (2020) Prevalence of alternative diagnoses and implications for management in idiopathic normal pressure hydrocephalus patients. Neurosurgery 87:999–1007. https://doi.org/10.1093/neuros/nyaa199
26. Mantovani G, Menegatti M, Scerrati A, Cavallo MA, De Bonis P (2018) Controversies and misconceptions related to cerebrospinal fluid circulation: a review of the literature from the historical pioneers' theories to current models. Biomed Res Int 2018:2928378–2928377. https://doi.org/10.1155/2018/2928378
27. Mattoli MV, Treglia G, Calcagni ML, Mangiola A, Anile C, Trevisi G (2020) Usefulness of brain positron emission tomography with different tracers in the evaluation of patients with idiopathic normal pressure hydrocephalous. Int J Mol Sci 21:6523. https://doi.org/10.3390/ijms21186523
28. Mirzayan MJ, Luetjens G, Borremans JJ, Regel JP, Krauss JK (2010) Extended long-term (> 5 years) outcome of cerebrospinal fluid shunting in idiopathic normal pressure hydrocephalus. Neurosurgery 67:295–301. https://doi.org/10.1227/01.NEU.0000371972.74630.EC
29. Miyajima M, Kazui H, Mori E, Ishikawa M (2016) One-year outcome in patients with idiopathic normal-pressure hydrocephalus: comparison of lumboperitoneal shunt to ventriculoperitoneal shunt. J Neurosurg 125:1483–1492. https://doi.org/10.3171/2015.10.JNS151894
30. Mori E, Ishikawa M, Kato T, Kazui H, Miyake H, Miyajima M, Nakajima M, Hashimoto M, Kuriyama N, Tokuda T, Ishii K, Kaijima M, Hirata Y, Saito M, Arai H (2012) Guidelines for management of idiopathic normal pressure hydrocephalus: second edition. Neurol Med Chir (Tokyo) 52:775–809. https://doi.org/10.2176/nmc.52.775
31. Nucci CG, De Bonis P, Mangiola A, Santini P, Sciandrone M, Risi A, Anile C (2016) Intracranial pressure wave morphological classification: automated analysis and clinical validation. Acta Neurochir 158:581–588. https://doi.org/10.1007/s00701-015-2672-5
32. Raneri F, Zella MAS, Di Cristofori A, Zarino B, Pluderi M, Spagnoli D (2017) Supplementary tests in idiopathic normal pressure hydrocephalus: a single-center experience with a combined lumbar infusion test and tap test. World Neurosurg 100:567–574. https://doi.org/10.1016/j.wneu.2017.01.003
33. Sindorio C, Abbritti RV, Raffa G, Priola SM, Germanò A, Visocchi M, Quattropani MC (2017) Neuropsychological assessment in the differential diagnosis of idiopathic normal pressure hydrocephalus. An important tool for the maintenance and restoration of neuronal and neuropsychological functions. Acta Neurochir Suppl 124:283–288. https://doi.org/10.1007/978-3-319-39546-3_41
34. Takeuchi T, Yajima K (2019) Long-term 4 years follow-up study of 482 patients who underwent shunting for idiopathic normal pressure hydrocephalus -course of symptoms and shunt efficacy rates compared by age group. Neurol Med Chir (Tokyo) 59:281–286. https://doi.org/10.2176/nmc.oa.2018-0318
35. Todisco M, Pozzi NG, Zangaglia R, Minafra B, Servello D, Ceravolo R, Alfonsi E, Fasano A, Pacchetti C (2019) Pisa syndrome in idiopathic normal pressure hydrocephalus. Parkinsonism Relat Disord 66:40–44. https://doi.org/10.1016/j.parkreldis.2019.06.024
36. Todisco M, Picascia M, Pisano P, Zangaglia R, Minafra B, Vitali P, Rognone E, Pichiecchio A, Ceravolo R, Vanacore N, Fasano A, Pacchetti C (2020) Lumboperitoneal shunt in idiopathic normal pressure hydrocephalus: a prospective controlled study. J Neurol 267:2556–2566. https://doi.org/10.1007/s00415-020-09844-x
37. Wikkelsø C, Hellström P, Klinge PM, Tans JTJ, European iNPH Multicentre Study Group (2013) The European iNPH Multicentre Study on the predictive values of resistance to CSF outflow and the CSF tap test in patients with idiopathic normal pressure hydrocephalus. J Neurol Neurosurg Psychiatry 84:562–568. https://doi.org/10.1136/jnnp-2012-303314