Parkinsonism and Related Disorders 66 (2019) 117–124

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

A prospective evaluation of clinical and instrumental features before and after ventriculo-peritoneal shunt in patients with idiopathic Normal pressure hydrocephalus: The Bologna PRO-Hydro study

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ARTICLE INFO

SEARCH TERMS:
Idiopathic Normal pressure hydrocephalus
Ventriculo-peritoneal shunt
Observational prospective study
Movement disorders
Neuropsychological features
Clinical practice

ABSTRACT

Introduction: Idiopathic Normal Pressure Hydrocephalus (iNPH) is a complex and often misdiagnosed syndrome, whose major challenge is to identify which patients will benefit from surgery. Previous studies reported a variability in positive surgery response. The role of tap test(TT) in screening patients suitable for shunting is controversial. The primary aim of this study was to describe the clinical/instrumental features and their longitudinal progression after surgery in iNPH patients. Secondarily, we aimed to investigate the response of the three iNPH domains and the best time of outcome assessment after TT.

Methods: Patients compatible with iNPH underwent a 3-T-MRI and an inpatients program with TT including standardized clinical evaluations, neuropsychological assessments and instrumental gait analysis pre- and after-(24-h and 72-h) TT. The multidisciplinary team selected candidates for surgery. Patients were evaluated 6- and 12-months after surgery.

Results: A total of 154 consecutive patients were included from 2015 to 2018, 76 with an iNPH diagnosis (43 underwent surgery, 35 were evaluated after 6-months). Clinical and instrumented quantitative gait measures and urinary symptoms improved over time along with some neuropsychological functions.

Concerning pre- and post-TT analyses, the three iNPH domains showed a different response after TT, the delayed motor assessment was more appropriate than the early one and the instrumental measures highlighted

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https://doi.org/10.1016/j.parkreldis.2019.07.021
Received 5 January 2019; Received in revised form 14 July 2019; Accepted 15 July 2019

the motor improvement.
Conclusion: iNPH patients improved after surgery, when accurately selected. A multidisciplinary team focused on this disease and a standardized protocol helped in achieving a correct diagnosis and management of iNPH. Our results could impact the management of this disease.

1. INTRODUCTION

Idiopathic Normal Pressure Hydrocephalus (iNPH) is a syndrome consisting of chronic ventricular dilation, normal cerebrospinal fluid (CSF) pressure and the symptomatic triad of dementia, gait dysfunction and urinary incontinence [1]. There is significant variation in the clinical presentation, severity and progression of these symptoms, and the entire triad needs not be present in order to consider a diagnosis of iNPH. Moreover, iNPH is a disease of the elderly population, it mimics other neurodegenerative disorders and could occur in patients with other neurological diseases (such as cerebrovascular disease or neurodegenerative disorders) and chronic comorbidities [2,3]. For these reasons, the diagnosis, and therefore management, of iNPH represents a challenge. The diagnosis is usually based on history, clinical findings, imaging data and CSF opening pressure but the gold standard remains clinical improvement after CSF shunting [2]. However, the short-term clinical benefit of shunt surgery has been estimated to range from 31% to 96% [4–8].A recent systematic review on the outcome of shunt surgery in iNPH patients reported positive short-term outcome in 71% of patients (range 28%–100%) after surgery [9]. This variability could be caused by the lack of internationally accepted methods for quantifying clinical outcomes but probably also by the heterogeneity of patient selection. To date, patient selection for CSF shunting is difficult and clinical, laboratory and instrumental predictors of a successful outcome are poorly understood [10].

The limitations and uncertainties associated with the clinical diagnosis have stimulated the search for more accurate methods for the selection of patients [2]. The CSF tap test (TT) is an inexpensive, readily available and safe predictive test but it showed controversial detection power and validity in screening patients suitable for shunting. Therefore, another unsolved issue in iNPH management is the role of the TT in predicting a good outcome after surgery. A systematic review [11] showed a specificity of 75% (range 33%–100%) and a sensitivity of 58% (range 26%–87%). The heterogeneous TT accuracy may be a consequence of the differences in studies' design, sample size, population characteristics, methods and outcome measures. A key source of this heterogeneity is the lack of standardization of TT methodology and of iNPH symptoms assessment with a variable amount of CSF removed (30–50 ml) [11], a lack of standardization of the outcome measures [11–14], and a different time of outcomes assessment among studies [11,13–18].

All these unsolved issues require clarification to better define the diagnosis of iNPH, to standardize the management of patients, to recognize patients who could benefit from surgery and to definitively identify factors predictive of positive outcome after surgery.

To these purposes, we conducted an observational prospective study investigating the clinical/instrumental features and their prognostic value in the outcome of surgery in a cohort of iNPH patients evaluated at IRCCS-Institute of Neurological Sciences of Bologna (the Bologna PRO-Hydro study).

We present an interim analysis of the Bologna PRO-Hydro study.

The primary aim of the present study was to describe the clinical/instrumental features and their longitudinal progression after surgery in our cohort of iNPH patients. Secondarily, we aimed to investigate the response of the three iNPH domains and the best time of outcome assessment after TT, and to determine a cut-off in TT response predicting the surgery outcome. .

2. METHODS

Inclusion criteria and the study method are detailed in the supplementary material. The study design is shown in Fig. 1. All patients referred to our Institute by neurologists, geriatricians, neurosurgeons and general practitioners with a suspicion of iNPH were evaluated. Prior to their assessment, the patients' medical charts and brain imaging available (MRI- or CT-scans) were reviewed by the multidisciplinary team (T0). Eligible patients underwent a 3-T-MRI specific protocol (T1). Neurologists or neurosurgeons evaluated patients in an outpatient visit (T2). Patients with clinical features and neuroimaging compatible with iNPH underwent the inpatient iNPH program with TT (T3) (Fig. 1). The diagnosis was assigned after reviewing all pre-TT clinical data and neuropsychological information, blood/CSF tests and comparisons between pre- and post- TT during a consensus case conference involving the multidisciplinary team. On the basis of the diagnosis, taking into consideration comorbidities and vascular risk factors, the multidisciplinary team established eligible patients for the ventriculo-peritoneal (VP) shunt (T4). A CT-scan was performed 1-day and 1-month after surgery (T5). Both groups of patients who underwent or not VP shunt were evaluated 6- and 12-months after surgery or after the inpatient iNPH program, respectively (T6-T7).

2.1. Standard protocol approval and patient consents

The study was conducted in agreement with the principles of good clinical practice. The study protocol was approved by the Local Ethics Committee of the local health service of Bologna, Italy (Cod. CE: 14131, 23/02/2015). All patients gave their written informed consent to study participation.

2.2. Statistical analysis

Normality of continuous parameters distribution was checked using the Skewness-Kurtosis test, variables were expressed as mean ± standard deviation (SD) or median along with interquartile ranges (IQR) when appropriate. Continuous variables were compared by using *t*-test or Wilcoxon rank-sum, as appropriate. Categorical variables were described by their absolute and/or relative frequencies and compared using Chi square test.

Repeated measures ANOVA was performed to investigate significant main effects for all patients across time (pre-TT, 24-h after TT, 72-h after TT, 6 months after VP shunt). Bonferroni post-hoc was performed for multiple comparisons between subgroups. Kruskall-Wallis test with Bonferroni post-hoc was utilized for multiple comparisons across time when appropriate. A p-value lower than 0.05 (2-sided) was considered significant. Statistical analyses were performed using the statistical software STATA®, version 14.0.

3. RESULTS

The study flow-chart is shown in Fig. 2. A total of 154 consecutive patients (94 males and 60 females) with suspected iNPH were referred to our Institute from May 2015 to May 2018. Of these, 145 patients (89 males and 56 females, 8 ongoing) were considered eligible for the Bologna PRO-Hydro Study, 137 (86 males and 61 females) underwent a 3-T-MRI and 89 patients (53 males and 36 females) were enrolled in the study and underwent the inpatient iNPH program. Finally, 76 patients (43 males and 33 females, age at evaluation: 74.80 ± 4.72) received a

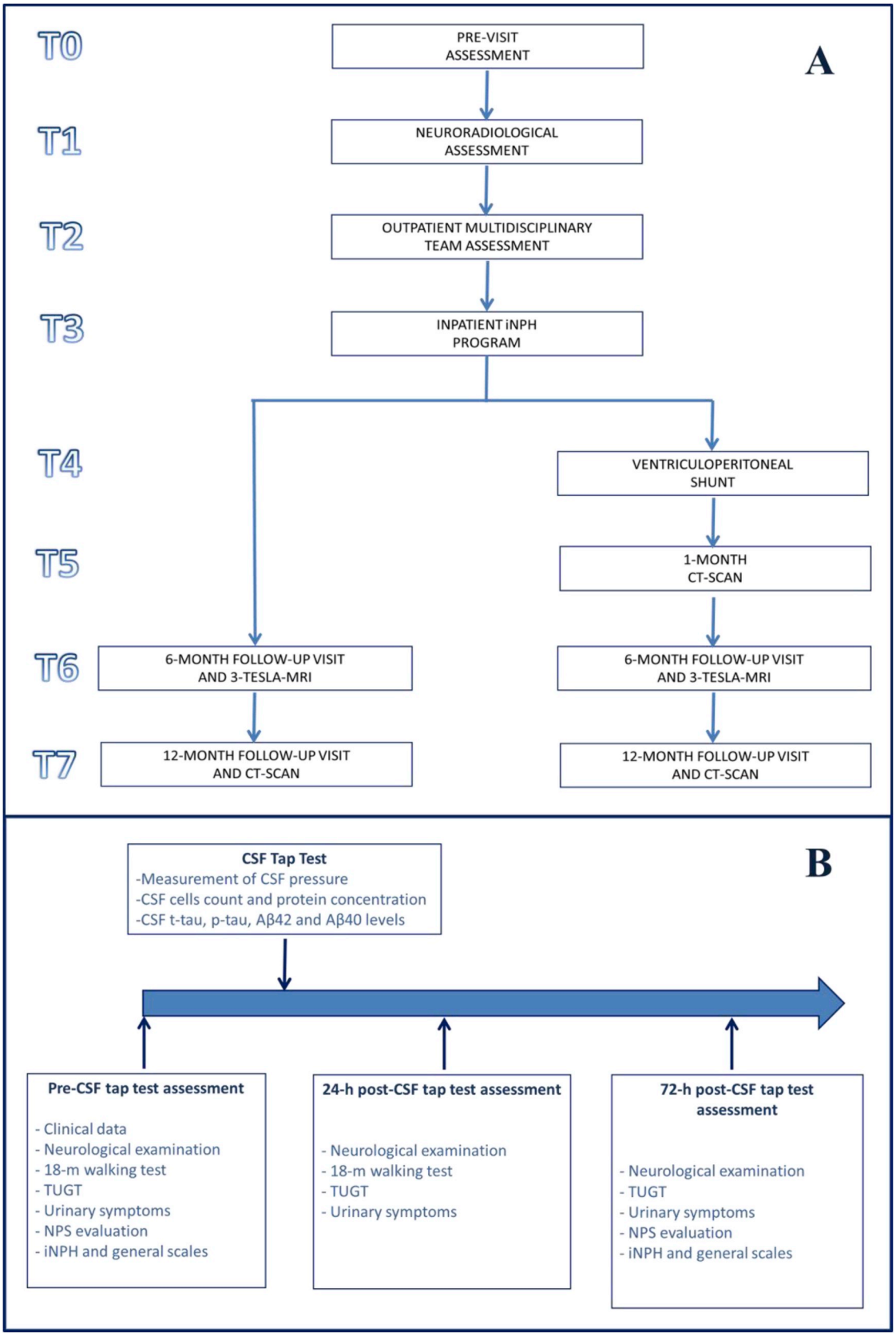

Fig. 1. Study design.
A: Study protocol; B: Inpatient iNPH program.
Legend = 18-m: 18-m; CSF: cerebrospinal fluid; CT: computerized tomography; MRI: magnetic resonance; NPS: neuropsychological evaluation; TUGT: timed up and go test.

diagnosis of iNPH. The multidisciplinary team considered 48 patients eligible for the VP shunt (28 were excluded for comorbidity or major contraindications), 43 of these underwent surgery (1 died from lymphoma, 1 refused surgery and 3 were ongoing). To date, 35 patients have undergone the 6-month follow-up visit after surgery (T6). Patient who refused VP shunt was followed up at the 6- and 12-month evaluations.

Out of 29 non-surgical patients, 18 underwent the 6-month follow-up visit (1 died from trauma complications, 1 was lost to the follow-up, 9 were ongoing).

A total of 15 (9.74%) patients dropped out: 7 declined to participate in the study, 7 refused the inpatient iNPH program, 1 was lost to the follow-up. A total of 46 of the initial 154 patients were excluded for other diagnoses: 27 were excluded after the MRI (9 with obstructive NPH and 18 with other diagnosis), 6 were excluded after the outpatient assessment, 13 were excluded after the iNPH program.

Demographic and clinical characteristics of the study sample are shown in Supplementary Table 1.

In our sample, age at disease onset was 71.87 ± 5.66 years with a disease duration of > 12 months in 72.37% patients. At the time of evaluation 52 (68.42%) patients showed the clinical triad while 18 (23.68%) and 6 (7.89%) showed 2 and 1 of the triad symptoms, respectively (Supplementary Table 1). All patients presented with gait disorders, 63 (82.89%) with urinary dysfunctions and 58 (76.32%) with cognitive impairment. The most frequent symptom at disease onset was gait disorder (65.79%), followed by balance disorder (17.11%), cognitive impairment (9.21%) and urinary dysfunctions (6.58%). On neurological examination 71.05% showed a wide-based gait, 68.42% heel height reduction, 55.26% arm swing reduction and 50% petit-pas gait. Bradykinesia was present in nearly half of patients while rigidity in about 30% of patients. Concerning the urinary domain, the most frequent urinary symptom was urinary urgency (81.58%) followed by urinary incontinence (67.11%), nycturia (64.47%) and pollakiuria (46.05%). Hypertension was the most frequent comorbidity with a prevalence of 63.16%. Hypercholesterolemia was present in 48.68%, diabetes in 39.47% and depression in 40.79%. Vascular encephalopathy was frequently observed in iNPH patients.

Mean scores of the neuropsychological test at baseline are reported in Table 1. The global cognitive performance of this sample was 24.49 ± 4.08 on the corrected Mini Mental State Evaluation, 29.41% of patients showed a pathological score. The final result of the Brief Mental Deterioration Battery was 0.32 ± 1.28 (pathological score in 25.76% of the sample). The cognitive profile of patients with iNPH revealed deficits in attentive and executive functions.

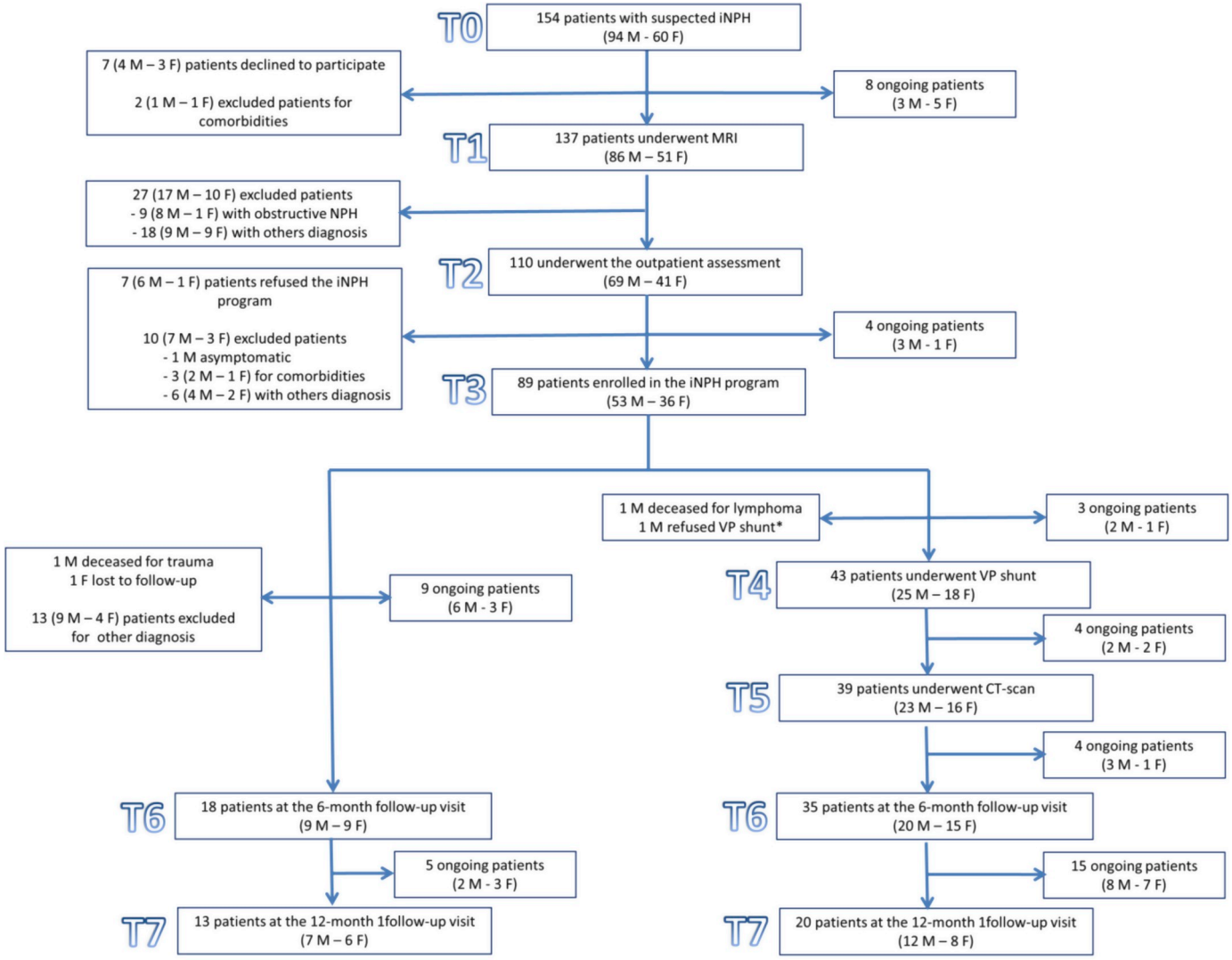

Fig. 2. Study flow-chart.
Legend = CT: computerized tomography; F: females; M: males; MRI: magnetic resonance; VP: ventriculo-peritoneal shunt; *Patient who refused VP shunt was followed up at the 6- and 12-month evaluations.

Table 1
Baseline neuropsychological profile in the iNPH sample.

	Cognitive functions explored	Total sample *n*	Score *mean ± SD*	Pathological Cut-off	Normal score *n (%)*	Pathological score *n (%)*
MMSEc	Global cognitive functions indices	68	24.49 ± 4.08	< 23.8	48 (70.59)	20 (29.41)
Brief Mental Deterioration Battery	Global cognitive functions indices	66	0.32 ± 1.28	≤0	49 (74.24)	17 (25.76)
Rey's 15 Words:	Memory					
immediate recall		68	32.14 ± 6.76	< 28.53	21 (30.88)	47 (69.12)
delayed recall		68	5.36 ± 4.84	< 4.69	14 (20.59)	54 (79.41)
Immediate Visual Memory	Memory	67	16.34 ± 4.55	< 13.85	44 (65.67)	23 (34.33)
Barrage Test	Attention					
time		67	**104.70 ± 53.25**	≥90	32 (47.76)	35 (52.24)
score		67	8.88 ± 3.10	≤9	34 (50.75)	33 (49.25)
errors		67	**2.55 ± 4.46**	≥2	44 (65.67)	23 (34.33)
final result		67	**4.44 ± 5.07**	> 2.5	31 (46.27)	36 (53.73)
Copy Design: simple	Constructional praxis	68	9.45 ± 2.49	< 7.18	36 (52.94)	32 (47.06)
Rey-Osterrieth Complex Figure Test	Constructional praxis - Visuospatial functions - Memory					
direct copy		63	**24.18 ± 10.99**	≤28.87	23 (36.51)	40 (63.49)
delayed recall		63	10.28 ± 5.06	≤9.46	16 (25.40)	47 (74.60)
Simple Verbal Analogies Test	Abstract/concrete thinking – intelligence	66	**13.81 ± 4.44**	≤13.92	31 (46.97)	35 (53.03)
Verbal Fluency	Language - Executive functions					
Phonemic		67	22.81 ± 8.68	< 17.35	33 (49.25)	34 (50.75)
Semantic		67	30.74 ± 10.21	< 25	30 (44.78)	37 (55.22)
Stroop test	Attention					
time		66	**33.04 ± 42.99**	> 27.5	35 (53.03)	31 (46.97)
errors		66	**10.46 ± 12.04**	> 7.5	36 (54.55)	30 (45.45)
Digit Span	Memory - Executive functions					
forward		62	5.31 ± 0.90	< 4.26	37 (59.68)	25 (40.32)
backward		64	3.42 ± 1.00	< 2.65	44 (68.75)	20 (31.25)
Corsi Block-tapping Test	Memory	64	3.85 ± 1.51	< 3.46	28 (43.75)	36 (56.25)
Frontal Assessment Battery	Executive functions Abstract/concrete thinking – intelligence	64	**11.50 ± 2.76**	≤13.4	8 (12.50)	56 (87.50)

MMSEc: corrected Mini-Mental State Examination; n: sample size; SD: standard deviation. See Supplementary Material for references of each test.

3.1. Clinical and instrumental outcomes post VP shunt

At 6 months 90.91% of patients reported a subjective global improvement and in 78.79% of cases this improvement was also reported by relatives. Quantitative motor performances pre-, 24-h and 72-h after TT, and 6-months after surgery of patients who underwent VP shunt are presented in Table 2. Patients who underwent VP shunt showed a global improvement in clinical quantitative gait measures (particularly total time on the TUGT, gait speed and step length on the 18-m walking test and number of steps at 180° turn) (Table 2). The Tinetti Assessment tool progressively increased showing a reduction in fall risk and this improvement was significant both at 72-h after TT and 6-months after VP shunt. Finally, an improvement of the urinary symptoms was observed at 72-h after TT and at 6-months after surgery (Table 2).

The modifications of instrumented 18-m walking test and TUGT pre-, 24-h after and 72-h after-TT, and 6 months after surgery of patients who underwent VP shunt are presented in Table 2. Both on the TUGT and 18-m walking test the majority of parameters significantly improved over time (total time, total steps, stride length, gait speed). The post-hoc analysis showed that this statistical significance was attributable to the difference between baseline and 6-month follow-up visit for all parameters and to the differences between 72-h after TT and baseline in some parameters (Table 2).

The neuropsychological evaluations pre-TT, 72-h after TT, and 6 months after surgery of patients who underwent VP shunt showed a significant improvement in Immediate Visual Memory, direct and delayed copy of Rey-Osterrieth Complex Figure (Supplementary Table 2). This statistical significance was attributable to the difference between 6 months after surgery and baseline evaluations. No test showed a significant improvement at 72-h after TT. Globally, an improvement in visual working and long-term memory was reported at 6 months after surgery.

3.2. Clinical response and time of outcome assessment after TT in all iNPH sample

Comparing quantitative motor performances pre-, 24-h after and 72-h after TT in all iNPH sample, our results demonstrated that, despite the progressive improvement of motor tests, the best performances were recorded at 72-h and not at 24-h (Supplementary Table 3). The TUGT time decreased from 22.63 ± 13.49 to 20.09 ± 13.52 s at 24-h and to 17.80 ± 7.27 s at 72-h with an overall $p = 0.0618$. Comparing the clinical motor performances on the 18-m walking test between pre- and 24-h post-TT there were no significant differences. The improvement on the Tinetti Assessment Tool, performed 72-h after TT, was significant ($p = 0.0003$).

The results obtained from instrumented 18-m walking test and TUGT pre-, 24-h after and 72-h after TT confirmed that better motor

Table 2
Clinical features and instrumented quantitative motor performances pre-, 24-h after and 72-h after-tap test and 6-months after surgery of patients underwent ventriculo-peritoneal shunt.

	Pre-TT tap test assessment	24-h after TT assessment	72-h after TT assessment	6-month follow-up visit	p-value
Clinical features					
TUGT [s]	23.64 ± 15.04	18.76 ± 6.02	17.30 ± 5.26°	15.84 ± 6.52*	**0.0028**
Time 18-m wt [s]	34.21 ± 25.30	28.32 ± 8.73		24.74 ± 8.27	0.0567
Number of steps (18-m wt)	48.72 ± 20.06	45.68 ± 13.26		41.41 ± 10.91	0.1500
Gait Speed (18-m wt) [m/s]	0.64 ± 0.21	0.68 ± 0.18		0.78 ± 0.22*	**0.0277**
Step length (18-m wt) [m]	0.41 ± 0.11	0.42 ± 0.10		0.48 ± 0.11*	**0.0180**
Number of steps (180° turn)	5.00 ± 2.76	4.94 ± 3.13		3.12 ± 1.41*	**0.0042**
Corrections during 8 steps at tandem walking	6.06 ± 2.86	5.84 ± 2.95		4.59 ± 3.23	0.1118
Number of urinary symptoms	2.55 ± 1.29	1.44 ± 1.16#	1.27 ± 1.27°	1.67 ± 1.43*	< **0.001**
Tinetti Assessment Tool	18.07 ± 6.21		22.24 ± 4.55°	23.94 ± 3.75*	< **0.001**
Instrumented quantitative motor performances					
TUGT					
Total Time [s]	22.28 ± 12.86	20.23 ± 8.38	20.74 ± 21.72	15.21 ± 4.45*	**0.0034**
Total Steps	25.03 ± 10.78	24.29 ± 10.15	24.40 ± 26.37	18.21 ± 4.70*	**0.0093**
Cadence Mean [steps/min]	48.30 ± 8.76	50.84 ± 10.49	51.36 ± 9.23°	52.17 ± 7.66*	**0.0219**
Stride length mean [cm]	63.89 ± 21.79	65.07 ± 19.32	69.92 ± 20.61°	77.55 ± 16.59*	< **0.0001**
Gait Speed mean [cm/s]	52.53 ± 20.24	57.17 ± 19.04	58.95 ± 19.23°	62.67 ± 18.68*	< **0.0001**
Turn steps	2.44 ± 1.48	2.40 ± 1.43	2.46 ± 2.99	1.85 ± 0.56	0.0757
18-m walking test					
Total Time [s]	31.28 ± 14.90	28.71 ± 10.33	26.26 ± 7.93	27.18 ± 11.43*	**0.0008**
Total Steps	39.91 ± 16.51	37.70 ± 8.80	34.38 ± 7.42°	35.03 ± 9.19*	**0.0146**
Cadence Mean [steps/min]	50.81 ± 7.97	52.13 ± 6.85	51.16 ± 5.18	53.36 ± 6.54	0.0694
Stride length mean [cm]	88.66 ± 22.61	90.24 ± 20.55	97.56 ± 18.93	97.87 ± 22.17*	**0.0086**
Gait Speed mean [cm/s]	75.84 ± 22.48	80.65 ± 22.70	87.38 ± 21.50°	84.61 ± 23.06*	< **0.0001**

Statistically significant p-values are denoted in bold (p value ≤ 0.05).
Legend = *: significant Bonferroni post-hoc test between 6-month visit and baseline; °: significant Bonferroni post-hoc test between 72-h after TT and baseline; #: significant Bonferroni post-hoc test between 24-h after TT and baseline; 18-m: 18-m; 18-m wt: 18-m walking test; cm: centimeters; h: hours; min: minutes; s: seconds; TT: tap test; TUGT: timed up and go test.

performances were recorded 72-h after the maneuver (Supplementary Table 3).

Comparing the urinary symptoms pre-, 24-h after and 72-h after TT there was a significant reduction in the number of urinary symptoms (2.59 ± 4.41, 1.49 ± 1.36, 1.32 ± 1.42,p < 0.0001) with a significant reduction both at 24-h and 72-h after TT. Neuropsychological assessments pre- and 72-h post-TT did not show any statistical improvement.

The small number of patients evaluated at 6-months after surgery (VP responders and non-responders) did not allow the analysis to determine a cut-off in TT response predicting the surgery outcome at this time.

4. Discussion

This observational prospective study on iNPH patients resulted in the following clinically relevant findings: 1) a multidisciplinary team focused on this disease and a standardized protocol helped in achieving a correct diagnosis and management of iNPH; 2) surgery improves motor and urinary symptoms and some neuropsychological functions with an impact on fall risk, quality of life and activities of daily living in iNPH patients, when accurately selected; 3) this iNPH cohort showed a heterogeneous clinical presentation and progression of symptoms, with some characteristic clinical and neuropsychological features; 4) the three domains of iNPH showed a different response after TT and the delayed motor assessment is more appropriate than the early one; 5) the instrumental motor measures highlighted the motor improvement when compared to the clinical measures.

First, the study flow-chart showed that, out of 154 patients referred to our Institute with at least one symptom of the classical triad and classified as eligible by the multidisciplinary team in the pre-visit assessment, only 76 patients received a diagnosis of iNPH. Although our protocol enrolled patients with less strict criteria to improve diagnostic sensitivity, this result confirms that iNPH is a disease of the elderly population, iNPH symptoms may be confounded with many other neurodegenerative diseases and a standardized protocol is necessary for the differential diagnosis to identify patients who could benefit from surgery.

Second, iNPH patients who underwent VP shunt showed a global improvement in quantitative gait measures, an improvement in urinary symptoms and a reduction in fall risk. Moreover, a significant improvement in visual working and long-term memory was observed. However, there is not a clear improvement of other cognitive domains, therefore further studies should be performed to confirm these findings. Globally, these improvements impact on the quality of life and activities of daily living, as observed by means of Functional Independence Measure scale.

Our clinical outcomes after VP shunt are consistent with previous studies reporting a short-term clinical benefit of shunt ranging from 31% to 96% [4–8]. A recent systematic review of 64 studies with 3063 patients reported improvement in functional performance in 71% of patients [9]. Finally, cognitive dysfunction responds differently and generally less than gait disturbance to surgical treatment [19].

Third, this iNPH cohort showed a heterogeneous clinical presentation and progression. At the time of evaluation 68.42% of patients showed the clinical triad and all patients presented with gait disorders. On neurological examination the majority of patients showed a wide-based gait and a heel height reduction. Concerning the urinary domain, the most frequent urinary symptom was urinary urgency followed by urinary incontinence, nycturia and pollakiuria. Globally iNPH patients were cognitively characterized by attentive and executive deficits not primarily dependent on their underlying motor impairment. Moreover, iNPH patients showed a high prevalence of comorbidities. These results confirmed those reported in previous studies [2,20] showing that symptoms are developed insidiously and generally occur between the sixth and eighth decade of life [21]. The complete triad is seen in

50–75% of cases, with gait and cognitive disturbances occurring in 80–95%, and urinary incontinence in 50–75% of cases [2]. Gait and balance impairment appear either before or concurrently with urinary incontinence or the onset of dementia. Gait disturbance is normally the first sign of iNPH and its severity is variable, thus the differential diagnosis from neurodegenerative disorders with motor involvement can be difficult [2]. Urinary incontinence usually follows gait abnormalities and almost always includes urinary urgency and frequency [22]. Dementia is rarely the first and foremost symptom of iNPH, although it is often present [22]. Symptoms of dementia in iNPH overlap with those of other dementias [23]. iNPH dementia is generally thought as a predominantly frontal, sub-cortical type of dementia, but not many studies have aimed at characterizing the type of cognitive deficits and, to date, results have been discordant [24–29].

Another result of this study is that at 72-h after TT, better motor performances were recorded: comparing quantitative motor performances pre-, 24-h after and 72-h after TT in all iNPH sample, our results demonstrated that, despite the progressive improvement of motor tests, the best performances are recorded at 72-h and not at 24-h. Therefore, the delayed motor assessment was more appropriate than the early one. This result was observed both in clinical and instrumental evaluations, even if it was more relevant when measured with mGait. In particular, the following were the parameters with the best improvement: total time, total steps, stride length and gait speed on the 18-m walking test and gait speed and cadence on the TUGT. Another good measure of the motor improvement could be the Tinetti Tool Assessment as it summarizes different gait parameters. These findings suggested that previous studies investigating the motor improvement at 6-h, 12-h, 24-h after TT could have underestimated the rate at which patients improved and this could reflect also in the discrepancy between TT response and VP shunt response [11,13–18,30]. Conversely, a significant reduction in the number of urinary symptoms emerged both at 24-h and 72-h after TT. No neuropsychological test improved at 72-h after TT evaluation and some tasks clinically worsened without reaching statistical significance. Despite the small sample of our study, these results suggested that the 72-h after-TT assessment did not clinically impact on the diagnostic work-up. Other studies took into consideration the time of assessment after TT. One study investigated gait analyses before and 2-h, 4-h, 6-h, 8-h, and 24-h after TT, suggesting that TT response can be evaluated at any time within the first 24 h [30]. Another study determined the time course of improvement after TT for single-task and dual-task walking, performing gait analysis prior and 1–8 h, 24 h, 48 h and 72 h after TT. The maximal increase in gait velocity was observed 24–48 h after the maneuver while for dual-task paradigms maximal improvement occurred later (48–72 h) [31]. A recent study focused on quantitative data from TUGT and 10-m walking test obtained before and 1 and 4 days after TT, showing that TUGT on day 1 had the highest diagnostic accuracy and that the delayed assessment on day 4 was not superior [32]. Our results suggested that urinary symptoms are the first to improve after TT, that the best improvement of motor performances was revealed at 72-h after TT and that the neuropsychological evaluations after TT did not impact on the diagnostic work-up. However, further studies in largest sample are needed to confirm these findings.

From a pathophysiological point of view, these findings of late improvements after-TT, when CSF theoretically is restored, could suggest that other mechanisms are involved. Both the improved vascular autoregulation in the periventricular areas (which were thought to contribute to the gait disorder in iNPH patients) and the enhanced capacity for metabolic clearance of vasoactive and/or neurotoxic metabolites could represent the pathophysiological substrates of delayed improvement after TT [31,32]. Moreover, a leakage from dura mater after the lumbar puncture should contribute to these findings.

Finally, the instrumental gait parameters highlight the motor improvement, then this simple and inexpensive performances measured by means of mobile gait analysis systems should be integrated in the clinical practice.

The strengths of our study are that all patients included in the study were seen and followed up in a single center with a systematic method and this guarantees the uniformity of data collection. Moreover, both clinical and instrumental gait parameters were collected, 3-T-MRI was performed in all patients and neuropsychological evaluations were systematically performed before and after TT by using parallel forms. This is one of the few studies taking into consideration the time of assessment after TT. The main limitations of the study include the small sample evaluated 6 months after surgery until today, the lack of systematic assessment of quality of life by specific scale, the variability in terms of time between inpatient program and VP shunt for feasibility reasons. In particular, we reported a time window ranging from 1 week to 2 months between inpatient program and VP shunt: this variability is ascribable to the clinical practice, to acute internal disease or comorbidities in these patients, and to the waiting list for admission to the neurosurgery unit. In conclusion, iNPH is a complex and often misdiagnosed syndrome and the major challenge is to identify which patients will benefit from shunt surgery. A multidisciplinary team focused on this disease with a standardized approach protocol including instrumental gait analysis helps in achieving a correct diagnosis and management of iNPH. This study deepens the knowledge of the clinical features and the neuropsychological profile of iNPH patients, shows their progression and suggests a different response of the three domains after TT. Finally, our results suggest that delayed motor assessment is more appropriate than the early one, the neuropsychological assessment at 72-h after TT is not necessary and the instrumental gait parameters enhance the motor improvement. Moreover, our results could positively impact on the clinical practice proposing a simplified iNPH protocol including urinary symptoms and motor performances assessment at 72-h after TT, a baseline neuropsychological evaluation and the integration of instrumented motor measures. Further studies on a larger sample are necessary to identify specific variables and the cut-off of motor/urinary improvement after TT predicting the outcome after surgery and to clarify their prognostic role.

Future direction of the Bologna PRO-Hydro study is aimed at describing the clinical/instrumental differences between VP shunt responders vs. non-responders, at identifying predictors of the outcome of surgery, at determining a cut-off in TT response predicting the surgery outcome, and at describing the long-term follow-up of iNPH patients.

Author contributions

- Dr. Giannini: conception and design of the study, acquisition, analysis and interpretation of data, drafting of the manuscript;
- Dr. Palandri: supervision of the study, acquisition and interpretation of data, drafting of the manuscript;
- PhD Ferrari: acquisition of data, analysis and interpretation of data;
- Dr. Oppi: acquisition of data, analysis and interpretation of data;
- Dr. Albini-Riccioli: acquisition of data and interpretation of data;
- Dr. Milletti: conception and design of the study, acquisition of data, analysis and interpretation of data;
- Dr. Mantovani: acquisition of data, analysis and interpretation of data;
- Dr. Magnoni: acquisition and interpretation of data;
- Prof. Chiari: contributions to conception and design of the study, critical revision of the manuscript;
- Prof. Cortelli: substantial contributions to conception and design of the study, critical revision of the manuscript.
- Dr. Cevoli: substantial contributions to conception and design of the study, acquisition of data, analysis and interpretation of data, supervision of the study, critical revision of the manuscript.

Disclosure

Dr. Giannini reports no disclosures.

Dr. Palandri reports no disclosures.

PhD Ferrari has a significant financial interest in mHealth Technologies, a company that may have a commercial interest in the results of this research.

Dr. Oppi reports no disclosures.

Dr. Albini-Riccioli reports no disclosures.

Dr. Milletti reports no disclosures.

Dr. Mantovani reports no disclosures.

Dr. Magnoni reports no disclosures.

Prof. Chiari has a significant financial interest in mHealth Technologies, a company that may have a commercial interest in the results of this research.

Prof. Cortelli reports no disclosures.

Dr. Cevoli received honoraria for speaking engagements or consulting activities from Teva.

5. Study funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.07.021.

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