Received: 14 June 2024 | Accepted: 14 November 2024

DOI: 10.1111/ene.16567

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Beyond early motor response: Longitudinal cognitive and gait assessments after extended lumbar drainage in normal pressure hydrocephalus

Stefano Caneva[1] | Mehrnaz Hamedani[1] | Alessandro Pesaresi[2] | Laura Mori[1,3] | Annalisa Marzi[1,3] | Lucia Pellegrino[1,3] | Paolo Merciadri[4] | Andrea Bianconi[4] | Gianluigi Zona[1,4] | Matteo Pardini[1,5] | Pietro Fiaschi[1,4]

[1]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), University of Genova, Genoa, Italy

[2]Neurosurgery Unit, Department of Neurosciences Rita Levi Montalcini, University of Turin, Turin, Italy

[3]Neurorehabilitation Unit, Department of Neuroscience, IRCCS Ospedale Policlinico San Martino, Genoa, Italy

[4]Department of Neurosurgery, IRCCS Ospedale Policlinico San Martino, Genoa, Italy

[5]Department of Neurology, IRCCS Ospedale Policlinico San Martino, Genoa, Italy

Correspondence
Matteo Pardini, Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), University of Genova, Genoa 16132, Italy.
Email: matteo.pardini@unige.it

Funding information
Ministero della Salute; Ministero dell'Istruzione, dell'Università e della Ricerca, Grant/Award Number: ECS00000035 and PE0000006

Abstract

Background: Idiopathic normal pressure hydrocephalus (iNPH) is a multifactorial progressive disease affecting cognition, gait, and urinary continence, potentially reversible, or at least improvable, by a prompt surgical intervention. Given its potential surgical improvement, it is crucial to determine who will benefit of a ventriculo-peritoneal shunt. To date, although several procedures are considered useful to diagnose iNPH, there is no agreement concerning the best timing of the clinical assessment or the role played by formal cognitive testing.

Methods: Thirty participants with suspected iNPH were assessed at baseline, 2, and 15 days after 24-h extended lumbar drainage (ELD). Timed Up and Go test (TUG), Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and Frontal Assessment Battery (FAB) were administered in order to quantify motor and cognitive performances. The TUG was used to assess clinical response to ELD.

Results: Our sample showed significant differences between baseline assessment and follow-ups in the majority of tests. Although some enhancements in performances appeared in the first post-ELD assessment, both treatment responders and non-responders showed better performances in the delayed assessment. Post hoc comparison found significant differences in each time point between the two groups.

Conclusions: These results emphasize the key role of performing multiple assessments post CSF drainage, as response can be more prominent in a delayed rather than an early phase.

KEYWORDS
cognitive assessment, extended lumbar drainage, longitudinal assessment, normal pressure hydrocephalus, responder

INTRODUCTION

Idiopathic normal pressure hydrocephalus (iNPH) is the most common form of adult hydrocephalus, characterized by cognitive deficits, gait disturbances, and urinary incontinence (Hakim's triad). In particular, motor impairment is usually the first sign to appear, featuring equilibrium and gait disturbances. The locomotion pattern is characterized by a low gait velocity, due to a diminished stride length, a diminished foot-to-floor clearance during swing phase, and a typical disruption of dynamic equilibrium, showing a broad-based gait and an outward rotation of the feet [1]. Concerning cognitive impairment, defined as a subcortical cognitive decline, given the involvement of this component of the brain [2], it emerged that deficits are extensive and involve attention, executive functions, memory, verbal fluency, working memory, psychomotor speed, and visuospatial functions [2–5].

As this is a potentially reversible condition, diagnostic accuracy is of paramount importance. Unfortunately, up to date, the gold standard for the diagnosis of iNPH is shunt response, which is also the treatment [6]. According to the literature, the response to shunt surgery varies between case series from 29% up to 90% [7, 8]: this disparity in reported results reflects the difficulty in selecting suitable patients for shunt surgery as many pathologies mimic the symptoms of iNPH. Existing iNPH guidelines, such as the latest Japanese iNPH guidelines [9], present several tests that can be used to help diagnose iNPH and quantify disability, for example, tap test (TT), infusion test (IT), extended lumbar drainage (ELD), and intracranial pressure monitoring (ICPM). Regrettably, all these procedures are invasive and might also have some negative effects on patient's performance—for example, back pain [10].

To date, the selection of iNPH patients for shunt placement can be based on the assessment of clinical response to ELD, namely the temporary CSF external drainage of at least 24 h, that is considered one of the best and most cost-effective procedures to apply [2, 6, 11–14]. Nonetheless, the use of ELD to guide patient's selection for surgery is fraught with difficulties, especially regarding the choice of the optimal timing of the response assessment and the relative clinical relevance of cognitive symptoms as well as the use of validated cutoffs for all tests. All of this makes the impact and accuracy of correct surgical selection of patients with iNPH even more debated.

After ELD, cognitive response is controversial: both Marmarou and colleagues and Mahr et al. did not find any improvement in neuropsychological tests, including MMSE, whereas Chotai et al. showed a significant enhance of MMSE scores [11, 13, 15]. These data are difficult to compare considering the differences in the paradigm they applied, although sharing a 72-h long CSF drainage: on one hand, in Marmarou et al. and Mahr et al., the reassessment happened right after the removal of the system; on the other hand, Chotai tested the patients every day during the drainage as well as the day after the system removal. Furthermore, there are inhomogeneities in the criteria applied in respect of the cutoffs of improvement in MMSE scores to define a drainage positive response—for example, an increase compared to baseline assessment of at least two points [13] or 10% [11]. These discrepancy highlights the lack of a common strategy to detect changes after ELD: a critical issue, also reported in Japanese guidelines [9].

The aim of our study was thus to evaluate the impact in the diagnostic accuracy of early and delayed cognitive and motor assessment after ELD in patients with suspected iNPH as an useful approach to identify clinical change after ELD. This approach could thus provide insights into the optimal timespan for reassessment, considering differences in timing and dynamics of clinical responses to ELD and the best brief cognitive protocol to use in this setting.

METHOD

Subjects

A total of 30 people (female: 12) who referred for consultation were enrolled in the study and included in this analysis. They gave informed consent to participate to the study, which was conducted according to the guidelines of the Declaration of Helsinki and approved by local committee (Comitato Etico Territoriale CER Liguria N. registro 378/2023).

Participants' mean age was 74.6 ± 6.38 years and their mean educational level was 9 ± 3.65 years. All patients were firstly evaluated by a neurologist or a neurosurgeon from the Departments of Neurology and Neurosurgery of the San Martino University Hospital in Genoa (Italy). Each patient was subjected to a baseline cognitive and motor assessment (T0), performed by, respectively, a neuropsychologist and a physiatrist. At a later time, they underwent a 24-h long ELD of CSF, followed by a second and third assessment after a mean of 2 ± 0.87 (T1) and 15.25 ± 2.55 days (T2).

Despite the invasiveness of ELD procedure, which can lead to several complications (e.g., restlessness, delirium, headache, and meningitis), in our sample, we only registered only one case of dizziness, that resolved spontaneously within a few hours.

Assessment

Static and dynamic balance performances have been investigated with the Timed Up and Go test (TUG) [16], a very popular test for assessing lower extremity performance, mobility, and fall risk. The score corresponds to the time in seconds that the participant takes to perform the task, thus lower scores indicate better performances.

In order to assess cognition, each evaluation included the following screening tests: Mini Mental State Examination (MMSE) [17]; Montreal Cognitive Assessment (MoCA) [18], and Frontal Assessment Battery (FAB) [19]. The MMSE is a widely used screening test and consists of subtests on orientation, memory, attention, praxis, and language. The MoCA serves similar purposes and assesses the same domains but also provides insights into the patient's executive functions. The FAB, instead, focuses on the examination of executive functions. While applying a comprehensive battery of neuropsychological tests is typically a better option, screening instruments are suggested by guidelines [9, 20].

Operative technique

A lumbar puncture was performed using sterile technique usually in the lumbar 4–5 interspinous space, with a large-bore Tuohy needle (14–16 gauge). After CSF spillage was confirmed, the stylet was removed, and a 17- to 18-gauge catheter was slowly introduced into the subarachnoid space for about 10 cm. Then the needle was withdrawn, and the drain was connected to an external CSF collection system, set at the mattress level of patient's bed. A loop was created in the catheter to relieve tension, and it was then secured over the patient's flank with sterile dressings. Patients were advised to maintain complete bed rest. Nursing staff were trained to adjust the placement of the drainage system as necessary to achieve an average drainage of 10 mL of CSF per hour and to avoid over drainage. After 24 h from EDL placement, the system was removed and, if no complications were observed, patients were regularly discharged.

Statistical analysis

Statistical analyses were performed using SPSS for Windows version 22. Data are presented as mean ± standard deviation or absolute numbers (percentages) for continuous and categorical variables, respectively. Kolmogorov–Smirnov tests were performed to test the normal distribution of the data.

Comparisons between pre- (T0) and post-ELD (T1 and T2) were made using repeated measures analysis of variance (ANOVA) with Bonferroni post hoc comparison to identify significant differences in the tests. The significance level for post hoc comparisons was set at 0.05. For ANOVA, effect sizes are reported as partial eta-squared value (η^2) and interpreted as negligible ($\eta^2 \leq 0.01$), small ($0.01 \leq \eta^2 < 0.06$), medium ($0.06 \leq \eta^2 < 0.14$), or large ($\eta^2 \geq 0.14$) magnitude effect.

Treatment responders (RSP) were defined by an improvement of 10% at the TUG independently for each time point compared to baseline and, conversely, those who did not reach this cutoff were labelled as non-responders (nRSP) [21]. Seventeen participants were RSP (male: 11; mean age: 73.94 ± 7.4; education: 9.06 ± 3.6) and 13 nRSP (male: 7; mean age: 75.46 ± 5; education: 8.92 ± 3.9). In order to compare quantitative data between the two groups, an independent samples t-test was used when the data were normally distributed; otherwise, a Mann–Whitney non-parametric analysis was applied when the data were not normally distributed.

RESULTS

Whole sample analysis

In the whole sample, a repeated-measures ANOVA found statistically significant differences across the three time points in TUG [$F(2, 58) = 2.68$, $p = 0.05$, $\eta^2 = 0.085$], MMSE [$F(2, 58) = 5.69$, $p = 0.006$, $\eta^2 = 0.164$], and MoCA scores [$F(2.58) = 2.12$, $p = 0.049$, $\eta^2 = 0.068$].

A post hoc pairwise comparison using the Bonferroni correction showed that none of the changes between the initial assessment and first follow-up (T1) or between the first (T1) and the second post-ELD assessments (T2) was statistically significant. In contrast, the changes in TUG ($p = 0.001$), MMSE ($p = 0.001$) and MoCA ($p = 0.042$) scores reached significance when comparing baseline and second follow-up (T2) performances.

Results are shown in the upper section of Table 1.

Results in responders and non-responders groups

Further investigations were conducted separating the RSP and nRSP groups. Regarding within group analysis, the application of a repeated-measure ANOVA highlighted differences in TUG [$F(2.32) = 7.578$, $p = 0.002$, $\eta^2 = 0.32$] as well as in MMSE [$F(2.32) = 3.813$, $p = 0.03$, $\eta^2 = 0.19$] within RSP group and in MMSE [$F(2.23) = 3.229$, $p = 0.05$, $\eta^2 = 0.21$] within nRSP group. Given that MMSE is the only test where both groups showed significant changes across time, a spaghetti plot displaying participants' changes (Figure S1) and individual data (Table S1) are provided in Supplementary Materials. Post hoc analysis showed one significant change when comparing baseline assessment and the first follow-up (T1), with RSP group presenting a significant improvement in TUG ($p = 0.038$), as expected given the definition of RSP based on TUG performances. No significant differences arose between T1 and T2 assessments. When comparing baseline and delayed (T2) scores, significant differences have been identified in TUG in the RSP group ($p = 0.001$) and in MMSE in both groups (RSP: $p = p = 0.03$; nRSP: $p = 0.033$).

Between-group analyses showed no differences in TUG and FAB performances at any time point. RSP and nRSP mean scores differed significantly in MMSE, at T0 ($p = 0.014$, 95% CI [−3.827, −0.480]) and at T1 ($p = 0.001$, 95% CI [−4.350, −1.369]), and in MoCA at each evaluation (T0: $p = 0.009$, 95% CI [−6.764, −1.055]; T1: $p = 0.008$, 95% CI [−7.571, −1.279]; T2: $p = 0.004$, 95% CI [−7.892, −1.432]). Results are shown in the lower section of Table 1 and in Figure 1.

Table 2 and Figure 2 show clinical scales changes for each post-ELD time point in comparison to the baseline assessment in both groups, highlighting different dynamics across time points. Regarding the motor task, the RSP group exhibits a linear trend, indicating that the improvement is already evident at T1 and remains stable at T2. In contrast, the nRSP group shows a slight worsening of performance initially, followed by a delayed improvement at T2. Taking into consideration cognition, T2 showed the biggest delta scores in every test in both groups. In MMSE the RSP group shows almost identical positive delta score at T1 and T2, whereas the nRSP group shows no difference with T0 performances at first, followed by a noticeable improvement at T2, reaching even a better delta score than RSP group. In MoCA, RSP group mean delta scores slightly increase across time; on the contrary, nRSP performances remain essentially stable from T1 to T2. In FAB both groups follow almost identical paths and the very small gap observed at T1 is filled at T2.

TABLE 1 Test scores and statistical comparisons in the whole sample and between responders (RSP) and non-responders (nRSP) for each test at different time points.

Test	T0	T1	T2	*F*	*p*	η^2	$p_{T0\text{-}T1}$	(95% CI)	$p_{T1\text{-}T2}$	(95% CI)	$p_{T0\text{-}T2}$	(95% CI)
Whole sample												
TUG	18.57 ± 9.05	17.77 ± 11.62	15.68 ± 7.26	2.68	**0.05***	0.085	0.61	(−2.405, 4.006)	0.147	(−0.780, 4.962)	**0.001****	(1.359, 4.424)
MMSE	26.07 ± 2.43	26.47 ± 2.41	27.33 ± 2.17	5.69	**0.006****	0.164	0.31	(−1.194, 0.394)	0.062	(−1.780, 0.047)	**0.001****	(−1.886, −0.647)
MoCA	19.6 ± 4.21	20.20 ± 4.66	20.57 ± 4.69	2.12	**0.049***	0.068	0.24	(−1.627, 0.427)	0.44	(−1.320, 0.587)	**0.042***	(−1.894, −0.039)
FAB	12.79 ± 3.11	12.86 ± 2.3	13.41 ± 2.7	1.28	0.28	0.042	0.89	(−0.955, 1.092)	0.067	(−1.289, 0.047)	0.21	(−1.432, 0.329)
RSP (*N* = 17) and nRSP (*N* = 13) groups												
TUG												
RSP	19.06 ± 9.88	15.1 ± 6.08	14.76 ± 7.6	7.58	**0.002****	0.32	**0.038***	(0.192, 7.736)	1.0	(−3.168, 3.826)	**0.001****	(1.876, 6.711)
nRSP	17.93 ± 8.18	21.27 ± 15.92	16.87 ± 6.91	1.95	0.16	0.14	0.76	(−11.054, 4.381)	0.38	(−3.078, 11.865)	1.0	(−2.0, 4.116)
p	0.74	0.17	0.44									
MMSE												
RSP	27 ± 2.32	27.71 ± 1.57	28 ± 1.59	3.81	**0.03***	0.19	0.27	(−1.750, 0.339)	1.0	(−1.313, 0.725)	**0.03***	(−1.917, −0.083)
nRSP	24.85 ± 2.07	24.85 ± 2.41	26.46 ± 2.57	3.23	**0.05***	0.21	1.0	(−2.064, 2.064)	0.27	(−4.064, 0.833)	**0.033***	(−3.109, −0.121)
p	**0.014***	**0.001****	0.053									
MoCA												
RSP	21.29 ± 3.2	22.12 ± 2.67	22.65 ± 3.12	2.52	0.09	0.14	0.54	(−2.399, 0.752)	1.0	(−2.350, 1.292)	0.07	(−2.802, 0.752)
nRSP	17.38 ± 4.44	17.69 ± 5.57	17.85 ± 5.11	0.19	0.83	0.015	1.0	(−2.773, 2.158)	1.0	(−1.902, 1.594)	1.0	(−2.610, 1.687)
p	**0.009****	**0.008****	**0.004****									
FAB												
RSP	13.59 ± 1.84	13.41 ± 2.18	14.12 ± 2.09	1.41	0.26	0.081	1.0	(−0.975, 1.328)	0.52	(−2.038, 0.626)	0.53	(−1.532, 0.473)
nRSP	11.91 ± 2.6	11.98 ± 3.97	12.49 ± 3.21	0.3	0.74	0.024	1.0	(−2.947, 2.804)	0.68	(−1.622, 0.604)	1.0	(−3.048, 1.886)
p	0.059	0.22	0.12									

Note: Right side of the table shows *p*-values and confidence interval (CI) from post hoc comparisons across different time points. *, $p < 0.05$; **, $p < 0.01$.
Abbreviations: FAB: Frontal Assessment Battery; MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment; T0: baseline assessment; T1: early assessment; T2: late assessment; η^2: partial eta-squared value, negligible ($\eta^2 \leq 0.01$), small ($0.01 \leq \eta^2 < 0.06$), medium ($0.06 \leq \eta^2 < 0.14$), or large ($\eta^2 \geq 0.14$) magnitude effects.
Values in bold indicate statistically significant *p*-values.

Therefore, motor and cognitive dynamics show different trajectories between RSP and nRSP groups. It is noteworthy that, in any case, both groups showed an increase in performances not only in comparison to baseline, but also to T1 scores, emphasizing even more the importance of a delayed retest in iNPH assessment protocol.

Cognitive drainage response irrespective from motor performance

We then evaluated the presence of cognitive improvement irrespective of the extent of motor response to obtain a comprehensive overview of all changes following CSF drainage. Participants were thus split based on an improvement of at least 3 points in the MMSE or at least 5 points in the MoCA [22, 23]. Table 3 shows RSP/nRSP rates for each time point according to these cutoffs: globally, 17 participants (56.7%) responded considering TUG cutoff (12 at T1 and 13 at T2), 10 participants (33.3%) considering MMSE score enhancements (5 in each time point), and 4 participants (13.3%) considering MoCA improvements (2 at T1 and 3 at T2). From a cognitive perspective, 12 subjects (40%) resulted RSP: 8 improved in MMSE, 2 in MoCA, and 2 in both tests.

Furthermore, we observed RSP/nRSP rates considering a motor or cognitive improvement in at least one time point as an ELD response. Thus, in our sample 22 participants (73.3%) responded positively based on TUG or MMSE improvements: specifically, 12 improved in TUG, 5 in

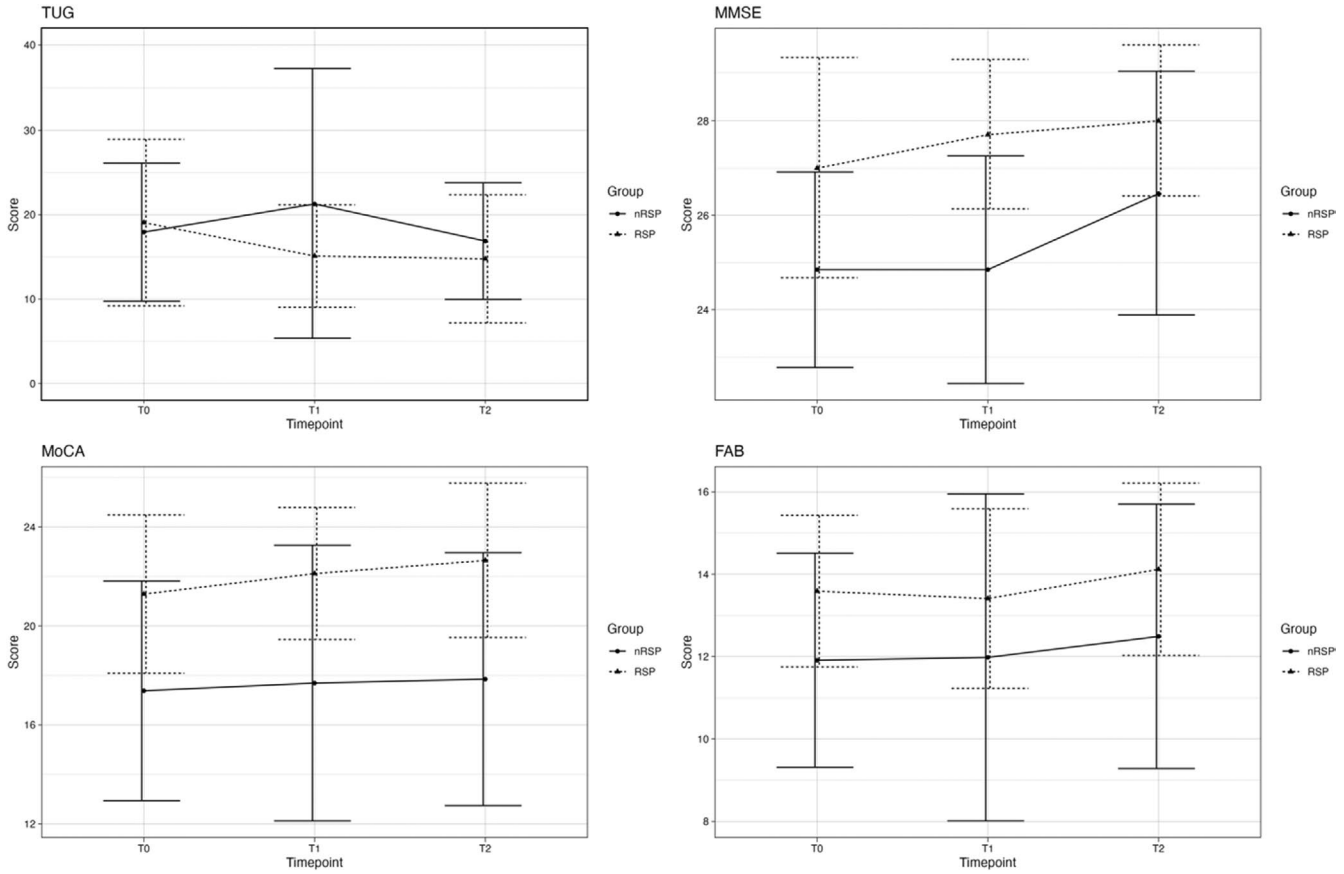

FIGURE 1 Graphs show means and standard deviations for responders (RSP) and non-responders (nRSP) for each test at different time points. As reported in the main text, the responder status is based on the TUG test.

TABLE 2 Mean ± standard deviation of delta scores in all tests in each time point in responders (RSP) and non-responders (nRSP) groups. TUG, Timed Up and Go test. MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; FAB, Frontal Assessment Battery; T1, early assessment; T2, late assessment.

Population	Test	ΔT1	ΔT2
RSP ($N = 17$)	TUG	−3.96 ± 5.82	−4.29 ± 3.73
	MMSE	0.71 ± 1.61	1 ± 1.41
	MoCA	0.82 ± 2.43	1.35 ± 2.23
	FAB	−0.18 ± 1.78	0.53 ± 1.55
nRSP ($N = 13$)	TUG	1.97 ± 12.97	−2.26 ± 8.2
	MMSE	0 ± 2.67	1.62 ± 1.93
	MoCA	0.31 ± 3.2	0.46 ± 2.79
	FAB	0.1 ± 3.7	0.5 ± 3.2

MMSE, and 5 in both parameters. Considering, instead, enhancements at TUG or MoCA, 20 participants (67%) responded: in particular, 16 improved in TUG, 3 in MoCA, and 1 in both parameters.

Considering these data, we observe different timings of response after CSF drainage, obtaining an earlier enhance in motor performance: specifically, 12 out of 17 among TUG RSP (70.6%) showed a significant improvement at T1, while this happened only in 5 out of 10 (50%) for MMSE and 2 out of 4 (50%) for MoCA.

DISCUSSION

The aim of our study was to observe differences between early and delayed cognitive and motor response after ELD in patients with suspected iNPH. Our findings regarding the whole sample revealed the importance of the latter, as all tests but FAB showed a significant improvement in T2 in comparison to baseline assessment.

Indeed, a notable symptom enhancement after ELD in comparison to baseline is a key aspect to assess possible surgery response to iNPH. However, the optimal timing for reassessing patients to check drainage response remains unclear. European guidelines provide no specific recommendations on the timing of retests following the drainage test, whereas Japanese ones state: "*it is recommended that the CSF tap test is evaluated within 24 hours after CSF removal and multiple evaluations should be done for up to a week. Cognitive impairment and urinary dysfunction are expected to improve subsequently after gait improvement, but there is no established evidence regarding the timing of this*" (p. 78) [9, 20]. As a consequence, studies have applied heterogeneous paradigms with different timespans between CSF removal and patients' revaluation.

Here we could find numerous significant improvements in performances dividing the sample into RSP and nRSP groups according to CSF drainage response in TUG. Specifically, comparing T1 and T0 performances indicated only TUG changes in RSP as significance,

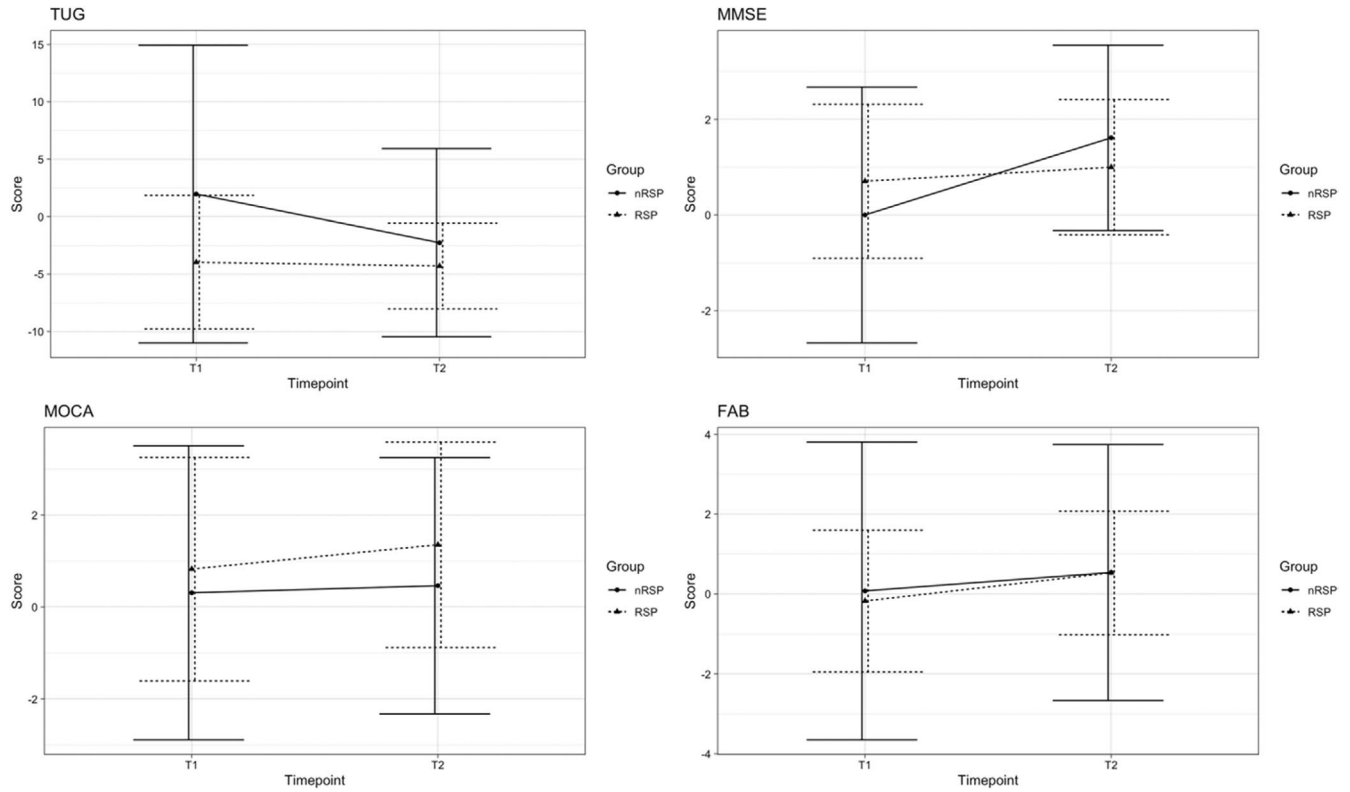

FIGURE 2 Graphs show means and standard deviations of score change compared to baseline (i.e., delta) for responders (RSP) and non-responders (nRSP) for each test at different time points compared to baseline. As reported in the main text, the responder status is based on the TUG test.

TABLE 3 Frequency (percentage) of responders (RSP) and non-responders (nRSP) for each test at different time points. As reported in the main text, here the responder status is based independently for each test. TUG, Timed Up and Go test; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment.

Test	Time point	RSP	nRSP
TUG			
	T1	12 (40%)	18 (60%)
	T2	13 (43.3%)	17 (56.7%)
	T1 or T2	17 (56.7%)	13 (43.3%)
MMSE			
	T1	5 (16.7%)	25 (83.3%)
	T2	5 (16.7%)	25 (83.3%)
	T1 or T2	10 (33.3%)	20 (66.7%)
TUG or MMSE		22 (73.3%)	8 (26.7%)
MoCA			
	T1	2 (6.7%)	28 (93.3%)
	T2	3 (10%)	27 (90%)
	T1 or T2	4 (13.3%)	26 (86.7%)
TUG or MoCA		20 (66.7%)	10 (33.3%)

whereas T2 and T0 comparison showed more complex results, with significant differences in TUG in RSP and in MMSE in both groups. Our findings highlight the need of a delayed response assessment, especially for cognition. Additionally, we noted that RSP scores at T2 continued to improve in every test administered, indicating a positive trend over time, whereas nRSP scores showed different trajectories (Figures 1 and 2). Nonetheless, in the delayed assessment the nRSP group showed a sharp improvement of the mean delta score not only in MMSE, but in TUG as well, indicating that also who did not reach the cut-off to be labelled as RSP benefits at a later time from CSF drainage in both motor abilities and cognition (Table 2 and Figure 2).

As shown in Table 1 and Figure 1, the RSP group exhibited better scores in cognitive tests with post hoc comparisons showing significant differences in MMSE (T0 and T1) and in MoCA (T0, T1, and T2). On the other hand, mean scores of this group are—not significantly—worse in TUG T0 assessment in comparison to the nRSP group: this might be due to the large standard deviation observed, but is in line with published databased on quantitative gait assessment, in which non-responders were moving faster than responders, pointing to a possible ceiling effect of motor measures [24]. Taken together, these findings suggest a potential association between cognitive and motor baseline outcomes and a positive response to ELD treatment.

Furthermore, our results expand previously published data and underline that cognitive improvement appears later after CSF drainage, consistent with Matsuoka et al. findings administering MMSE 7 days after TT [25].

The temporal discrepancy between motor and cognitive tests response after drainage is interesting and provides a window on the pathological mechanism underling neurological deficits in iNPH. Evidence from functional neuroimaging studies points to a role played

by altered network connectivity in iNPH as a key factor in cognitive and motor deficits in iNPH, with different networks underling different symptoms [26]. Cognitive tests, such as MMSE, used in this study are thought to probe extensive cortical networks and this could perhaps explain the latency observed in the cognitive response [6, 27]. Future studies combining longitudinal functional imaging are needed to better explain this observation.

A second key message of our study is represented by the characterization of subjects with isolated cognitive or motor responses based on brief cognitive assessment. Indeed, in addition to the TUG cutoff that we utilized, some authors suggested to consider differences in cognitive outcomes to discern between those who responded or not to CSF drainage [22]. When applied to our sample, this led to a notable discrepancy of RSP/nRSP rate: cognitive RSP in at least one assessment post-ELD were 40%, whereas motor RSP were 56.7%, as showed in Table 3. A partial explanation for this gap comes from the structure of the tests applied: whereas TUG score represents the time taken to execute the task, MMSE and MoCA scores have a range of 0–30, thus patients who obtain baseline scores equal or above 28 or 26, respectively, cannot reach the cutoffs applied in this study and therefore are labelled as nRSP. In our sample, this was true for 6 (20%) considering MMSE and 1 (3.3%) considering MoCA. This represents a nodal point that must be tackled in order to prevent cognitive responders from being misidentified due to the application of unspecific instruments, rather than a lack of improvements, since we have a partial knowledge of the changes happening in iNPH brain dynamics.

It is important to underline that the 3-point cutoff MMSE that we applied to define cognitive responders (showed in Table 3) is considered as a clinically meaningful improvement [28]. In other terms, in our sample, a total of 10 participants showed a clinically relevant enhance in global cognitive status after ELD treatment.

As a side note, we showed that FAB is not a suitable test to assess cognitive changes in iNPH. This is in line with the focus of this scale on the cortical prefrontal functions, while the underling physiopathology of neurophysiological deficits in iNPH is represented by multiple partial disconnections due to the involvement of deep white matter tracts.

Some limitations need to be considered in this study, starting with the limited sample size.

Despite the limited numerosity of our sample, the focus on subjects from a single center with dedicated clinicians and standardized procedure, increases results reliability. Indeed, our sample size is comparable to previous studies, highlighting the complexity in the formal study of these patients. Although we advised patients to continue with their regular lifestyle, we cannot exclude that some of them underwent physical training between the assessments, possibly biasing the observations. Another limitation is represented by the lack of a finer grained neuropsychological battery, which however was outside the scope of this work. Future studies with increased samples sizes are warranted, also focusing on neuropsychological profiling, other facets of iNPH, such as urinary symptoms which were not recorded in this work, and negative outcomes of treatment, especially focusing on back pain impact after lumbar puncture as a possible confounding factor [10]. Other open issues, outside the scope of this work and that are warranted to be explored in future studies, are the impact of the different post-ELD outcomes assessments to long-term post-surgery trajectories and the possible role of learning effects. It must be noted that learning effects on screening tests in INPH tests have been reported to be very limited and could thus represent one of its cognitive features; however, this needs to be formally assessed using multiple parallel groups [29].

In conclusion, ELD applied to patients with suspect iNPH is an effective diagnostic tool to evaluate motor and cognitive response, which allows to distinguish between RSP and nRSP. It is furthermore crucial to apply both motor and cognitive tests and to repeat at least twice the same assessment after CSF drainage: in this study, we showed that treatment response has a dynamic nature, highlighted by the differences found in the performances between the two post-ELD evaluations, pointing to a key role to extended follow-up in this population. Indeed, ELD can be considered a short-term shunt, and most patients usually show improvements also up to 2 weeks after the procedure, whereas after TT the effects usually disappear rapidly. [29] Future studies based on the same time points as our current study could help in better characterize the differences between these two approaches.

AUTHOR CONTRIBUTIONS

Stefano Caneva: Conceptualization; investigation; visualization; writing – original draft. **Mehrnaz Hamedani:** Data curation; formal analysis. **Alessandro Pesaresi:** Resources; writing – original draft. **Laura Mori:** Resources; supervision; writing – review and editing; methodology. **Annalisa Marzi:** Investigation. **Lucia Pellegrino:** Investigation. **Paolo Merciadri:** Resources. **Andrea Bianconi:** Resources. **Gianluigi Zona:** Funding acquisition; writing – review and editing. **Matteo Pardini:** Funding acquisition; resources; supervision; writing – review and editing. **Pietro Fiaschi:** Conceptualization; methodology; supervision; resources; writing – review and editing; funding acquisition.

FUNDING INFORMATION

This study was supported by Italian Ministry of Health (5x1000). MH was supported for this work by #NEXTGENERATIONEU (NGEU) and funded by the Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), and project MNESYS (PE0000006)—(DN.1553 11.10.2022). MP was supported for this work by #NEXTGENERATIONEU (NGEU) and funded by the Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), and project RAISE (ECS00000035)—(DN. 1053 del 23.06.2022).

CONFLICT OF INTEREST STATEMENT

The authors declared no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supporting information of this article.

ORCID

Stefano Caneva https://orcid.org/0000-0002-4064-6936
Laura Mori https://orcid.org/0000-0003-2762-8327

REFERENCES

1. Stolze H, Kuhtz-Buschbeck JP, Drücke H, et al. Gait analysis in idiopathic normal pressure hydrocephalus - which parameters respond to the CSF tap test? *Clin Neurophysiol*. 2000;111(9):1678-1686. doi:10.1016/S1388-2457(00)00362-X
2. Skalický P, Mládek A, Vlasák A, De Lacy P, Beneš V, Bradáč O. Normal pressure hydrocephalus—an overview of pathophysiological mechanisms and diagnostic procedures. *Neurosurg Rev*. 2020;43(6):1451-1464. doi:10.1007/s10143-019-01201-5
3. Bugalho P, Alves L, Miguel R, Ribeiro O. Profile of cognitive dysfunction and relation with gait disturbance in Normal pressure hydrocephalus. *Clin Neurol Neurosurg*. 2014;118:83-88. doi:10.1016/j.clineuro.2014.01.006
4. Hellström P, Klinge P, Tans J, Wikkelsø C. The neuropsychology of iNPH: findings and evaluation of tests in the European multicentre study. *Clin Neurol Neurosurg*. 2012;114(2):130-134. doi:10.1016/j.clineuro.2011.09.014
5. Saito M, Nishio Y, Kanno S, et al. Cognitive profile of idiopathic Normal pressure hydrocephalus. *Dement Geriatr Cogn Disord Extra*. 2011;1(1):202-211. doi:10.1159/000328924
6. Thavarajasingam SG, El-Khatib M, Rea M, et al. Clinical predictors of shunt response in the diagnosis and treatment of idiopathic normal pressure hydrocephalus: a systematic review and meta-analysis. *Acta Neurochir*. 2021;163(10):2641-2672. doi:10.1007/S00701-021-04922-Z/FIGURES/3
7. Hebb AO, Cusimano MD. Idiopathic normal pressure hydrocephalus: a systematic review of diagnosis and outcome. *Neurosurgery*. 2001;49(5):1166-1186. doi:10.1097/00006123-200111000-00028
8. Krauss JK, Droste DW, Vach W, et al. Cerebrospinal fluid shunting in idiopathic normal-pressure hydrocephalus of the elderly: effect of periventricular and deep white matter lesions. *Neurosurgery*. 1996;39(2):292-300. doi:10.1097/00006123-199608000-00011
9. Nakajima M, Yamada S, Miyajima M, et al. Guidelines for Management of Idiopathic Normal Pressure Hydrocephalus (third edition): endorsed by the Japanese Society of Normal Pressure Hydrocephalus. *Neurol Med Chir (Tokyo)*. 2021;61(2):63-97. doi:10.2176/nmc.st.2020-0292
10. Virhammar J, Cesarini KG, Laurell K. The CSF tap test in normal pressure hydrocephalus: evaluation time, reliability and the influence of pain. *Eur J Neurol*. 2012;19(2):271-276. doi:10.1111/j.1468-1331.2011.03486.x
11. Mahr CV, Dengl M, Nestler U, et al. Idiopathic normal pressure hydrocephalus: diagnostic and predictive value of clinical testing, lumbar drainage, and CSF dynamics. *J Neurosurg*. 2016;125(3):591-597. doi:10.3171/2015.8.JNS151112
12. Nunn AC, Jones HE, Morosanu CO, et al. Extended lumbar drainage in idiopathic normal pressure hydrocephalus: a systematic review and meta-analysis of diagnostic test accuracy. *Br J Neurosurg*. 2021;35(3):285-291. doi:10.1080/02688697.2020.1787948
13. Chotai S, Medel R, Herial N, Medhkour A. External lumbar drain: a pragmatic test for prediction of shunt outcomes in idiopathic normal pressure hydrocephalus. *Surg Neurol Int*. 2014;5(1):12. doi:10.4103/2152-7806.125860
14. Bianconi A, Colonna S, Minardi M, et al. Prognostic factors in idiopathic Normal pressure hydrocephalus patients after Ventriculo-peritoneal shunt: results from a single-institution observational cohort study with long term follow-up. *World Neurosurg*. 2024;187:e1089-e1096. doi:10.1016/j.wneu.2024.05.060
15. Marmarou A, Young HF, Aygok GA, et al. Diagnosis and management of idiopathic normal-pressure hydrocephalus: a prospective study in 151 patients. *J Neurosurg*. 2005;102(6):987-997. doi:10.3171/jns.2005.102.6.0987
16. Podsiadlo D, Richardson S. "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc*. 1991;39(2):142–148. doi:10.1111/j.1532-5415.1991.tb01616.x
17. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695-699. doi:10.1111/j.1532-5415.2005.53221.x
18. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a frontal assessment battery at bedside. *Neurology*. 2000;55(11):1621-1626. doi:10.1212/wnl.55.11.1621
19. Relkin N, Marmarou A, Klinge P, Bergsneider M, Black PM. Diagnosing idiopathic Normal-pressure hydrocephalus. *Neurosurgery*. 2005;57(3):S2-S16. doi:10.1227/01.NEU.0000168185.29659.C5
20. Ishikawa M, Hashimoto M, Mori E, Kuwana N, Kazui H. The value of the cerebrospinal fluid tap test for predicting shunt effectiveness in idiopathic normal pressure hydrocephalus. *Fluids Barriers CNS*. 2012;9(1):1. doi:10.1186/2045-8118-9-1
21. Wesner E, Etzkorn L, Bakre S, et al. The clinical utility of the MOCA in iNPH assessment. *Front Neurol*. 2022;13:887669. doi:10.3389/fneur.2022.887669
22. Gallina P, Lastrucci G, Caini S, Lorenzo ND, Porfirio B, Scollato A. Accuracy and safety of 1-day external lumbar drainage of CSF for shunt selection in patients with idiopathic normal pressure hydrocephalus. *J Neurosurg*. 2018;131(4):1011-1017. doi:10.3171/2018.6.JNS18400
23. Passaretti M, Maranzano A, Bluett B, Rajalingam R, Fasano A. Gait analysis in idiopathic Normal pressure hydrocephalus: a meta-analysis. *Mov Disord Clin Pract*. 2023;10(11):1574-1584. doi:10.1002/mdc3.13816
24. Matsuoka T, Akakabe M, Iida JI, Kawahara M, Uchiyama Y. Changes in cognitive function scores after cerebrospinal fluid tap testing in patients with suspected idiopathic Normal-pressure hydrocephalus. *Cogn Behav Neurol off J Soc Behav Cogn Neurol*. 2018;31(4):201-206. doi:10.1097/WNN.0000000000000176
25. Griffa A, Bommarito G, Assal F, Herrmann FR, Van De Ville D, Allali G. Dynamic functional networks in idiopathic normal pressure hydrocephalus: alterations and reversibility by CSF tap test. *Hum Brain Mapp*. 2021;42(5):1485-1502. doi:10.1002/hbm.25308
26. Bonney PA, Briggs RG, Wu K, et al. Pathophysiological mechanisms underlying idiopathic Normal pressure hydrocephalus: a review of recent insights. *Front Aging Neurosci*. 2022;14:866313. doi:10.3389/fnagi.2022.866313
27. Hensel A, Angermeyer MC, Riedel-Heller SG. Measuring cognitive change in older adults: reliable change indices for the mini-mental state examination. *J Neurol Neurosurg Psychiatry*. 2007;78(12):1298-1303. doi:10.1136/jnnp.2006.109074
28. Solana E, Poca MA, Sahuquillo J, Benejam B, Junqué C, Dronavalli M. Cognitive and motor improvement after retesting in normal-pressure hydrocephalus: a real change or merely a learning effect? *J Neurosurg*. 2010;112(2):399-409. doi:10.3171/2009.4.JNS081664
29. Toma AK. Extended lumbar drainage: supplementary test to diagnose shunt responsive iNPH. In: Bradac O, ed. *Normal Pressure Hydrocephalus: Pathophysiology, Diagnosis, Treatment and Outcome*. Springer International Publishing; 2023:209-219. doi:10.1007/978-3-031-36522-5_12

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Caneva S, Hamedani M, Pesaresi A, et al. Beyond early motor response: Longitudinal cognitive and gait assessments after extended lumbar drainage in normal pressure hydrocephalus. *Eur J Neurol*. 2025;32:e16567. doi:10.1111/ene.16567