Timed up and go test at tap test and shunt surgery in idiopathic normal pressure hydrocephalus

Shigeki Yamada, MD, PhD; Masatsune Ishikawa, MD, PhD; Masakazu Miyajima, MD, PhD; Madoka Nakajima, MD, PhD; Masamichi Atsuchi, MD, PhD; Teruo Kimura, MD, PhD; Takahiko Tokuda, MD, PhD; Hiroaki Kazui, MD, PhD; Etsuro Mori, MD, PhD

Abstract

Background: The 3-meter Timed Up and Go test (TUG) is a reliable quantitative test for assessment of gait and balance. We aimed to establish an optimal threshold of TUG at the tap test for predicting outcomes 12 months after shunt surgery in patients with idiopathic normal pressure hydrocephalus (iNPH). **Methods:** The TUG was measured in a total of 151 patients with possible iNPH before and after a tap test and 12 months after shunt surgery. Among them, 81 patients underwent ventriculoperitoneal shunt implantation (SINPHONI) and 70 underwent lumboperitoneal shunt implantation (SINPHONI-2). The areas under the curve (AUCs), sensitivities, and specificities for predicting shunt effectiveness were assessed.

Results: The simple differences of time on TUG at the tap test were significantly more accurate for predicting shunt effectiveness than percent improvement of time. The highest AUC for the synchronized moving cutoff point of TUG time was 0.81 (sensitivity 81.0%; specificity 81.6%) at the threshold of 5 seconds in the SINPHONI-2. For predicting improvements of ≥ 10 seconds 12 months after lumboperitoneal shunt implantation, the AUC was 0.90, and the sensitivity and specificity at the threshold of 5.6 seconds were 83.3% and 81.0%. Only for patients with a < 5 -second improvement at the tap test, ventriculoperitoneal shunt implantation conveyed significantly better improvements in TUG time 12 months after surgery than lumboperitoneal shunt implantation. **Conclusions:** An improvement of 5 seconds was a useful threshold of TUG time at the tap test for predicting a ≥ 10 -second improvement 12 months after shunt surgery, rather than the percent improvement of TUG time. *Neurol Clin Pract* 2017;7:98-108

Normal Pressure Hydrocephalus Center (SY, MI), Department of Neurosurgery, Rakuwakai Otowa Hospital, Kyoto; Department of Neurosurgery (MM, MN), Juntendo University Graduate School of Medicine, Tokyo; Department of Neurosurgery (MA), Atsuchi Neurosurgical Hospital, Kagoshima; Department of Neurosurgery (TK), Dohtoh Neurosurgical Hospital, Hokkaido; Department of Molecular Pathobiology of Brain Diseases (Neurology) (TT), Kyoto Prefectural University of Medicine; Department of Psychiatry (HK), Osaka University Graduate School of Medicine; and Department of Behavioral Neurology and Cognitive Neuroscience (EM), Tohoku University Graduate School of Medicine, Miyagi, Japan.

Coinvestigators are listed at Neurology.org/cp.

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Correspondence to: shigekiyamada39@gmail.com.

The diagnosis and management of idiopathic normal-pressure hydrocephalus (iNPH) has progressed since the establishment of current international and Japanese guidelines.^{1–5} These guidelines recommend a tap test as a supplemental examination for predicting a response to shunt surgery.^{1–14} However, there is no universally concordant method for assessing the severity of symptoms related to iNPH and the response to the tap test and shunt surgery. The 3-meter Timed Up and Go test (TUG) is widely used as a reliable quantitative test for assessment of gait and balance in patients with iNPH.^{6,10,13,15–22} The Japanese Society of Normal Pressure Hydrocephalus has proposed a $\geq 10\%$ reduction of time on the TUG as a quantitative indicator of gait improvement in iNPH.^{1,2,4} However, the sensitivity and specificity of the proposed threshold of TUG has not proven sufficiently reliable for clinical usage.

Previously, we demonstrated efficacy of ventriculoperitoneal shunts in the study of iNPH on neurologic improvement (SINPHONI) and lumboperitoneal shunts in SINPHONI-2 for the patients with possible iNPH.^{6,23–27} Because all of the participants in these studies underwent shunt surgery, irrespective of their response to the tap test, accurate sensitivity and specificity measurements for predicting outcome of shunt surgery can be calculated. The purpose of the present study was to identify an optimal cutoff value on the TUG at the tap test for predicting outcome in common with SINPHONI and SINPHONI-2. In addition, the predictability of the tap test for improving the TUG after ventriculoperitoneal shunt surgery was compared with that after lumboperitoneal shunt surgery.

METHODS

Standard protocol approvals, registrations, and patient consents

In SINPHONI (NCT00221091), 100 patients diagnosed with possible iNPH were enrolled between 2004 and 2006. All of them underwent a tap test and ventriculoperitoneal shunt surgery, and outcomes were evaluated through 12 months postsurgery. In SINPHONI-2 (UMIN000002730), 93 patients with possible iNPH were enrolled between 2010 and 2011. Then, 45 patients were randomly assigned to undergo lumboperitoneal shunt implantation within 1 month of randomization and 38 patients were assigned to postpone lumboperitoneal shunt implantation for 3 months after randomization. All participants in both groups of SINPHONI-2 underwent a tap test after randomization and were followed up to 12 months post shunt surgery.

All of the clinical and radiologic data have been prospectively recorded in an independent protocol compliance center. The institutional review boards at each study site approved the study design and protocol of SINPHONI and SINPHONI-2, which conformed to the Guidelines for Good Clinical Practice and the Declaration of Helsinki of the World Medical Association. All patients or their representatives gave written informed consent. Details of the participants, variable definitions of iNPH, protocol compliance, and data collection protocols, including data acquisition and management, were described in our prior publications.^{6,23–27} In brief, patients diagnosed with congenital hydrocephalus, aqueductal stenosis, secondary NPH, or concomitant diseases with severe disuse muscle atrophy, lumbar deformation, or narrow spinal canals were excluded from this study. Due to deficits in TUG data before or after the tap test, or at 12 months after shunt surgery, 19 patients in SINPHONI and 13 patients in SINPHONI-2 were excluded from analyses in this article. Thus, 81 patients in SINPHONI and 70 patients in SINPHONI-2 were ultimately analyzed for sensitivity and specificity of the TUG.

Measurement and evaluation of the TUG

All patients underwent a tap test, which involved ≥ 30 mL removal of CSF via a lumbar tap. The time (in seconds) on the TUG was measured before and within 24 hours after the tap test, and at follow-up examinations 3, 6, and 12 months after shunt surgery. For the TUG test (video at Neurology.org/cp), the patients had to stand up from an armless chair and walk a distance of 3 meters as quickly as was safely possible. Once they reached a line indicating 3-meter distance, they turned 180 degrees, walked back to the chair, and sat down as quickly as possible.

Video

Neurology.org/cp

The simple differences in time on TUG at the tap test were significantly more accurate for predicting shunt effectiveness than percent improvement of time.

Percent improvement of time on the TUG was calculated as (TUG time before tap test – TUG time after tap test or shunt surgery)/TUG time before tap test $\times$ 100 (%). Potential cutoff points of 10%, 15%, 20%, 25%, and 30% improvement of time on the TUG were assessed. In addition, the simple difference of time on the TUG was calculated as TUG time before tap test – TUG time after tap test or shunt surgery.

The time difference on the TUG was categorized as worse, <5-second improvement, $\geq$ 5- to <10-second improvement, and $\geq$ 10-second improvement for convenience of clinical usage. For the sensitivity and specificity analyses, potential cutoff points of the time difference were set from 1 to 7 seconds.

At first, the cutoff points of percent improvement and simple difference of time on the TUG were used not only for the assessment of the tap test but also for shunt surgery as a synchronized moving cutoff point. Specifically, a patient who improved $\geq$ 10% in TUG time after the tap test was assessed as having a predictive effect of $\geq$ 10% improvement in the TUG time 12 months after shunt surgery.

Second, we assessed the optimal cutoff points for the tap test after setting 10% or 10 seconds in the improved TUG time for the shunt surgery, because a $\geq$ 10-second improvement could be regarded as a sufficient improvement 12 months after shunt surgery. Positive detection ratio was defined as a frequency of the patients judged as having positive response to the tap test in each cutoff point.

Statistical analysis

Median values and interquartile ranges (IQRs) for age at entry, time on the TUG before and after the tap test, time difference, and improved percentage of TUG after the tap test in the groups comprising SINPHONI and SINPHONI-2 were analyzed using the Mann-Whitney *U* test. The frequencies in each category of TUG time before and after the tap test, time difference, and improved percentage in TUG time were compared between SINPHONI and SINPHONI-2 by the χ^2 test. The receiver operating characteristic (ROC) curve for the ability of TUG time at the tap test to predict shunt effectiveness was plotted, and the area under the ROC curve (AUC) was calculated to maximize the sum of the sensitivity and specificity. Two AUCs were compared by the DeLong test.²⁸ In addition, to elucidate the causes for the differences of the accuracy of the tap test between SINPHONI and SINPHONI-2, the odds ratios (ORs), 95% confidence intervals, and probability (*p*) values of a Fisher exact test were calculated. A sufficient response to the tap test was defined as $\geq$ 5 seconds of the improved TUG time, whereas a poor response to the tap test was defined as worse or <5-second improvement in this study. To assess predicting outcomes 12 months after shunt surgery, a fairly good outcome was defined as $\geq$ 5- to <10-second improvement in the TUG time, and a clinically sufficient outcome was defined as $\geq$ 10-second improvement, in comparison to worse or <5-second improvement. In each group of patients with or without response to the tap test, the ORs for 1-year shunt effectiveness were calculated after adjusting for age at entry in the logistic regression analyses. Statistical significance was assumed at a probability of *p* < 0.05. All missing data were treated as deficit data not affecting other variables. All statistical analyses were performed using R software (version 3.0.1; R Foundation for Statistical Computing, Vienna, Austria; R-project.org).

Table 1 Change in time on the Timed Up and Go test (TUG) before and after the tap test

	Total	SINPHONI (VP shunt)	SINPHONI-2 (LP shunt)
Total patients	151	81	70
Male	85 (56.3)	47 (58.0)	38 (54.3)
Age, y	76 (72–79)	75 (71–78)	77 (73–80)
TUG time before tap, s	19 (14.4–26)	20 (15–26)	16.9 (13–24.7)
<10	7 (4.6)	3 (3.7)	4 (5.7)
≥10 and <15	33 (21.9)	12 (14.8)	21 (30.0)
≥15 and <20	40 (26.5)	24 (29.6)	16 (22.9)
≥20 and <30	40 (25.9)	27 (33.3)	13 (18.6)
≥30	31 (20.5)	15 (18.5)	16 (22.9)
TUG time after tap, s	15.2 (11.7–21)	16 (12–21)	14.2 (11–19.2)
<10	22 (14.6)	7 (8.6)	15 (21.4)
≥10 and <15	47 (31.1)	26 (32.1)	21 (30.0)
≥15 and <20	40 (26.5)	22 (27.2)	18 (25.7)
≥20 and <30	23 (15.2)	16 (19.8)	7 (10.0)
≥30	19 (12.6)	10 (12.3)	9 (12.9)
Time difference of TUG at tap	3.0 (1.0–6.1)	3.0 (1.0–6.0)	3.0 (1.5–6.8)
Worse	16 (10.6)	7 (8.6)	9 (12.9)
<5 seconds improved	79 (52.3)	44 (54.3)	35 (50.0)
≥5 and <10 seconds improved	36 (23.8)	19 (23.5)	17 (24.3)
≥10 seconds improved	20 (13.2)	11 (13.6)	9 (12.9)
Improved percentage of TUG time at tap	17.9 (6.7–29.2)	15.4 (6.7–27.6)	20 (8.9–30.5)
Worse	16 (10.6)	7 (8.6)	9 (12.9)
<10% improved	30 (19.9)	21 (25.9)	9 (12.9)
≥10 and <20% improved	32 (21.2)	17 (21.0)	15 (21.4)
≥20 and <30% improved	35 (23.2)	17 (21.0)	18 (25.7)
≥30% improved	38 (25.2)	19 (23.5)	19 (27.1)

Abbreviations: LP = lumboperitoneal; VP = ventriculoperitoneal.

Values are median (interquartile range) or n (%).

RESULTS

There were no differences between the SINPHONI and SINPHONI-2 (table 1) groups in the median values of the time or frequency of categories in time on the TUG before and after the tap test, nor was there a significant difference in the changes in time on the TUG at the tap test. Median age was different ($p = 0.021$), with the SINPHONI group median age being 2 years younger than in the SINPHONI-2 group. There were more patients who completed the TUG within 10 seconds after the tap test in the SINPHONI-2 group than in the SINPHONI group. The frequency of scores in the other TUG time categories was similar between the SINPHONI and SINPHONI-2 groups before and after the tap test. Specifically, the frequency of time difference on the TUG at the tap test was very similar between the 2 groups, as follows: about 10% showing a worsening, ≥50% showing a <5-second improvement, 24% showing a ≥5- to <10-second improvement, and 13% showing a ≥10-second improvement (table 1).

Table 2 Synchronized moving cutoff points for percentage improvement and time difference (seconds) on the Timed Up and Go test after the tap test and 12 months after shunt surgery

Cutoff point	SINPHONI (VP shunt)			SINPHONI-2 (LP shunt)		
	AUC	Sensitivity, %	Specificity, %	AUC	Sensitivity, %	Specificity, %
10%	0.554	37.1	73.7	0.625	85.0	40.0
15%	0.579	50.8	65.0	0.686	77.1	60.0
20%	0.569	59.3	54.5	0.679	73.3	62.5
25%	0.569	38.8	75.0	0.718 ^a	68.0	75.6
30%	0.589	32.5	85.4	0.660	50.0	82.0
1 second	0.511	17.6	84.6	0.676	91.1	44.0
2 seconds	0.528	33.3	72.2	0.688	89.2	48.5
3 seconds	0.552	56.1	54.2	0.748	81.2	68.4
4 seconds	0.568	48.1	65.5	0.747	76.0	73.3
5 seconds	0.567	43.2	70.3	0.813 ^b	81.0	81.6
6 seconds	0.627	40.0	85.4	0.772	66.7	87.8
7 seconds	0.625	36.1	88.9	0.785	65.0	92.0

Abbreviations: AUC = area under the receiver operating characteristic curve; LP = lumboperitoneal; VP = ventriculoperitoneal.

^aThe highest AUC in the category of improved percentage in the TUG time.

^bThe highest AUC in the category of time difference on the TUG.

In AUC analyses using synchronized moving cutoff points (table 2), the highest AUCs were 0.72 (sensitivity 68.0%; specificity 75.6%) at the threshold of 25% and 0.81 (sensitivity 81.0%; specificity 81.6%) at the threshold of 5 seconds in SINPHONI-2. In SINPHONI, however, there were no AUCs of ≥ 0.63 in any threshold categories. Positive detection rates for $\geq 25\%$ and ≥ 5 -second improvements in TUG time at the tap test were 33.3% and 37.0% in SINPHONI and 40.0% and 37.1% in SINPHONI-2, respectively.

The ROC curves to compare the accuracy of the tap test for predicting $\geq 10\%$ and ≥ 10 -second improvements on the TUG in each group of SINPHONI and SINPHONI-2 are shown in the figure, A and B. The simple differences in time on TUG at the tap test were significantly more accurate for predicting shunt effectiveness than percent improvement of time. Especially, the AUC for predicting ≥ 10 -second improvement 12 months after lumboperitoneal shunt implantation in the SINPHONI-2 was 0.90, and the sensitivity and specificity at the threshold of 5.6 seconds at the tap test were 83.3% and 81.0%.

The sensitivity, specificity, and positive detection rates for the synchronized moving cut-off point of time difference on the TUG at the tap test for predicting improvement 12 months after shunt surgery are shown in the figure, C. The curves of specificities and positive detection rates in SINPHONI and SINPHONI-2 completely overlapped each other. As the threshold of improved time changed from 1 to 7 seconds, the specificities were gradually increased from $<30\%$ to $>80\%$, and the positive detection rates were decreased from $>75\%$ to $<25\%$. The sensitivities in SINPHONI gradually decreased in keeping with $\geq 20\%$ lower than those in SINPHONI-2 with the thresholds moving from 1 to 5 seconds of improvement in the time on the TUG. The times at the crossover of the sensitivity and specificity curves were between 4 and 5 seconds in the SINPHONI group and between 5 and 6 seconds in the SINPHONI-2 group. Therefore, 5 seconds was determined to be the optimal cutoff time on TUG at the tap test for predicting sufficient improvement on the TUG 12 months after shunt surgery in common with SINPHONI and SINPHONI-2.

Figure Receiver operating characteristic (ROC) curves and sensitivity/specificity decision plot for predicting shunt effectiveness by the Timed Up and Go test (TUG) at the tap test

ROC curves for the comparison between a ≥ 10 -second improvement (solid lines) and a $\geq 10\%$ improvement (dashed lines) in the time on the TUG 12 months after ventriculoperitoneal (VP) shunt in SINPHONI (A) and after lumboperitoneal (LP) shunt in SINPHONI-2 (B). Half transparent lines indicate the fitted smooth binormal curves. The candidates for the optimal cutoff points (sensitivities, specificities) are marked at the black points. The sensitivity/specificity decision plot (C) shows sensitivities (triangular marks), specificities (circle marks), and positive detection rates (quadrangular marks) at the maximum area under the ROC curve (AUC) for the synchronized moving cut-off point in SINPHONI (dashed lines) and SINPHONI-2 (solid lines).

Table 3 demonstrates the relationship between improved time on the TUG after the tap test and at 12 months after shunt surgery in the SINPHONI and SINPHONI-2 groups. Among the patients whose TUG time after the tap test had either worsened or improved by < 5 seconds, 40 of 44 patients (90%) in SINPHONI-2 remained unimproved or improved < 5 seconds on the TUG 12 months after lumboperitoneal shunt implantation, but half of the patients improved ≥ 5 seconds 12 months after ventriculoperitoneal shunt implantation in SINPHONI. This was the cause for lower sensitivity on the TUG at the tap test for predicting outcome in the SINPHONI cohort. For the patients with a poor response to the tap test, the expectation of a ≥ 5 -second or ≥ 10 -second improvement 12 months after ventriculoperitoneal shunt implantation was significantly higher than it was after lumboperitoneal shunt

The international guideline for prevention of falls in frail elderly individuals recommends TUG as a screening tool for increased risk of falls.

implantation. However, for the patients with a ≥ 5 -second improvement in TUG time at the tap test, either lumboperitoneal or ventriculoperitoneal shunt implantation had the same expectation of improvement on the TUG, with probability of $\geq 60\%$ for a ≥ 5 -second improvement and about 40% for a ≥ 10 -second improvement 12 months after surgery.

DISCUSSION

TUG has been increasingly used as indicator of gait disturbance throughout the world,^{18,19,29–37} beginning with the proposal of Podsiadlo and Richardson³⁸ that TUG could serve as a modified version of the Get-up and Go test introduced by Mathias et al. The international guideline for prevention of falls in frail elderly individuals recommends TUG as a screening tool for increased risk of falls.³⁹ Previous studies have suggested that elderly individuals scoring ≥ 20 seconds on the TUG have a significantly higher risk for falls, whereas < 10 seconds on the TUG indicated normal physical performance.^{29–37}

The Japanese Society of Normal Pressure Hydrocephalus proposed $\geq 10\%$ improvement in time on the TUG as a cutoff point for the tap test,^{1,2,4} because the simple difference in time on the TUG would be disadvantageous to the patients with mild gait disturbance. For example, it seems to be more difficult for patients with < 20 seconds of time on the TUG before the tap test to improve by 5 seconds at the tap test or shunt surgery, compared to patients with ≥ 20 second TUG times. Indeed, in this study, 13 of 80 patients (16.3%) with < 20 second TUG times before the tap test decreased their time by ≥ 5 seconds after the tap test, whereas 43 of 71 (60.6%) with ≥ 20 seconds decreased their time by ≥ 5 seconds. Furthermore, all 31 patients who improved ≥ 10 seconds on the TUG 12 months after shunt surgery had a TUG time of

Table 3 Comparison of improvement time on the Timed Up and Go test 12 months after ventriculoperitoneal (VP) shunt vs lumboperitoneal (LP) shunt in each tap test response subgroup

	SINPHONI, VP shunt, n (%)	SINPHONI-2, LP shunt, n (%)	AOR (95% CI)	p Value ^a
Worse or < 5 seconds improved at tap test (n = 95)				
Total number	51	44		
Worse or < 5 seconds improved	26 (51)	40 (90)	Reference	
≥ 5 and < 10 seconds improved	18 (35)	2 (5)	14.6 (3.05–70.3)	< 0.001
≥ 10 seconds improved	7 (14)	2 (5)	7.10 (1.26–40.1)	0.027
≥ 5 seconds improvement at tap test (n = 56)				
Total number	30	26		
Worse or < 5 seconds improved	11 (37)	9 (35)	Reference	
≥ 5 and < 10 seconds improved	7 (23)	7 (27)	0.82 (0.21–3.23)	0.779
≥ 10 seconds improved	12 (40)	10 (38)	1.06 (0.30–3.69)	0.929

Abbreviations: AOR = age-adjusted odds ratio; CI = confidence interval.

^aProbability value for Fisher exact test.

≥ 20 seconds before the tap test. On the contrary, the percent improvement of TUG time was rarely influenced by the TUG time before the tap test. More than 10% improvement 12 months after shunt surgery was observed in 49 patients (61.3%) with < 20 seconds and 53 patients (74.6%) with ≥ 20 seconds on the initial TUG times. However, the percent improvement of time on the TUG at the tap test did not have sufficient accuracy in predicting improvement on the TUG 12 months after shunt surgery. We therefore concluded that the simple difference of time on the TUG at the tap test was useful and more accurate for predicting improvement of TUG time following shunt surgery than percent improvement of time. We found that the greater the decrease in TUG time after the tap test, the more one could expect improvement in physical performance after shunt surgery.

The possibility of a false-negative response to the tap test cannot be eliminated. The tap test was previously reported to have high specificity (73%–100%) but low sensitivity (26%–79%) for predicting effectiveness of ventriculoperitoneal shunt surgery in patients with possible iNPH.^{6–12} In this study, the sensitivity for predicting improvement of TUG time 12 months after ventriculoperitoneal shunt implantation in the SINPHONI cohort was lower than it was for lumboperitoneal shunt implantation in the SINPHONI-2 cohort. The main reason for this relatively lower sensitivity in the case of ventriculoperitoneal shunt implantation, which is essentially the same as a high false-negative rate, might be that more of the patients receiving ventriculoperitoneal shunt surgery, who did not respond to the tap test, improved unpredictably compared to those who underwent lumboperitoneal shunt surgery. In contrast, the response to the tap test was correlated with the response to lumboperitoneal shunt implantation. Directly reducing intraventricular volumes and compression of the periventricular brain by the ventricular drainage of CSF might act on the extra improvement of gait and balance associated with TUG time in some patients with iNPH who did not sufficiently improve after the spinal tap. However, we do not have a definitive explanation for the discrepancy between the response to lumbar and ventricular drainage. Performance on the TUG was reported to be significantly associated with not only age, walking speed, lower extremity weakness, and balance disorder, but also cognitive impairment.^{13,33,40} Cognitive impairment associated with iNPH was reported to improve to lesser degree after that tap test than in shunt surgery cases.^{5,6,10,13,20} We did not assess the confounding effects of improving cognitive impairment after shunt surgery, because the number of each tap-test response subgroup is small and lacks the power of statistical analysis, especially multivariate analysis. The other limitation of our study is lack of a direct comparison between ventriculoperitoneal and lumboperitoneal shunt surgery. The participants in the SINPHONI-2 underwent cervical and lumbar MRI to evaluate spinal canal stenosis for the indication of lumboperitoneal shunt implantation, but those in the SINPHONI did not. Therefore, some patients in the SINPHONI might have had concurrent cervical canal stenosis or experienced adverse events, such as orthostatic headache or pains in the back or legs, just after the tap test. Further studies investigating the discrepancy between the response to lumbar and ventricular drainage and the effect of cognitive impairment on the change in time on the TUG at the tap test are warranted.

In conclusion, we found that simple difference in time on the TUG was better than the percentage change in time for evaluating improvement after the tap test or shunt surgery in iNPH. In addition, we found that an improvement of ≥ 5 seconds on the TUG at the tap test was a highly accurate predictive factor for improvement of ≥ 10 seconds on the TUG 12 months after shunt surgery. In contrast, some patients exhibiting a poor response to the tap test displayed more improvement in physical performance if they received a ventriculoperitoneal shunt rather than a lumboperitoneal shunt, as indicated by the TUG. These findings imply that the TUG should be recommended as a reliable and simple quantitative examination tool for evaluating improvement in gait disturbance and physical performance after the tap test or shunt surgery in iNPH, especially in patients with ≥ 20 second TUG times before the tap test. Patients with < 20 second TUG times need the other test for a quantitative evaluation of changes in gait disturbance specific to iNPH.

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AUTHOR CONTRIBUTIONS

M.I. and E.M. conceived the study, coordinated the study, and chaired the steering committee. All authors were members of the steering committee and designed and wrote the study protocol with input from all listed members of the study advisory board (coinvestigators available at Neurology.org/cp). All authors were involved in the interpretation and/or presentation of the data, reviewed and revised the initial draft and subsequent versions of the report, and approved the submitted version. All listed investigators contributed to enrollment of patients. The steering committee and independent data and safety monitoring committee monitored the study. S.Y. wrote the first draft.

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