Movement Disorders
CLINICAL PRACTICE
REVIEW

Gait Analysis in Idiopathic Normal Pressure Hydrocephalus: A Meta-Analysis

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Abstract: Background: Gait analysis objectively quantifies gait impairment in idiopathic normal pressure hydrocephalus (iNPH), may improve diagnosis and evaluation for surgical candidacy.
Objectives: This meta-analysis aims to understand which objective gait parameters improve after tap-test (TT) and CSF shunt surgery (CSS), also comparing responders (R) with non-responders (NR) and to assess if gait restores within the range of healthy controls after procedures.
Methods: Studies enrolling iNPH with at least one instrumented gait measure were selected. Three time points of gait assessment were defined: PRE, POST-TT, and POST-CSS. Gait velocity, cadence, step length, stride length, and double limb support time were evaluated. Patients were categorized based on responsiveness to CSF diversion procedures.
Results: Seventeen studies including 527 patients were selected. iNPH improved significantly in almost all gait parameters POST-TT, and to a greater extent POST-CSS. Gait parameters consistently discriminated iNPH from healthy controls. Despite the aforementioned improvements, iNPH's gait did not completely normalize after CSF diversion procedures. Meta-regression analysis also revealed that TT's effect on gait velocity plateaus after 24–48 hr and returns to baseline in 90–100 hr.
Conclusions: Gait analysis is a reliable quantitative instrument to assess gait impairment in iNPH, demarking a net differentiation from healthy controls, according to the notion that the iNPH CSF dynamic alteration also leads to an irreversible damage. Specific gait parameters improve among TT-R, providing an opportunity to select patients that will respond to CSS. Future studies validating a standardized reporting method including criteria of responsiveness, specific gait parameters, and timeframe of assessment are needed.

Normal Pressure Hydrocephalus (NPH) is a clinical entity characterized by the symptomatic triad of gait and balance impairment, subcortical cognitive impairment, and urinary incontinence associated with enlarged brain ventricles under normal (or slightly elevated) cerebral spinal fluid pressure. When no overt cause is found (e.g., subarachnoid hemorrhage or meningitis), NPH is considered "idiopathic" (iNPH), although criticisms about the use of this term have been recently raised.[1] Improvement of this condition after the placement of a cerebrospinal fluid (CSF) shunt constitutes the prominent feature of the syndrome. Patients eligible for shunt intervention are selected usually based on the clinical response to a "tap test" (TT), a procedure consisting of the removal of about 30–50 mL of CSF via lumbar puncture. External lumbar CSF drainage is less often used due to its invasiveness although it features a better diagnostic accuracy.

Gait issues are usually the first symptoms to appear and the most frequently observed among iNPH patients.[2] The main typical gait abnormalities reported are represented by hypokinetic, broad-based walking with reduced speed and step length in

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variable association with start hesitation, freezing of gait, festination, and postural instability.[3,4]

Gait is clinically assessed before and after TT usually by a neurologist, neurosurgeon, or physiotherapist, although no uniform method has been adopted and tandem gait, timed up and go, retropulsion tests, and other subjective measures of balance are variably utilized. Therefore, the evaluation of gait impairment and response to TT is poorly standardized and rater-dependent, with the risk of missing subtle improvements.

Gait analysis is an established method of quantitative assessment for gait disturbances.[5] Considering that gait impairment is the most sensitive clinical feature to respond to TT, it is crucial to collect accurate and objective data before and after the TT to better determine which patients are likely to benefit from shunt placement. Early identification of these patients can lessen the impact of iNPH on brain parenchyma, thus reducing the severity of disability caused by a delayed diagnosis.[6] Although these evidences suggest the importance of quantitative gait analysis in the management of iNPH, currently no reviews or meta-analyses specifically investigating this topic have been published.

The aim of this meta-analysis is threefold: (1) to quantify the improvement in objective gait parameters after TT and CSF shunt surgery (CSS) in iNPH; (2) to compare the gait of iNPH patients with healthy controls at baseline and after TT and/or CSS; (3) to quantify the differences in objective gait parameters between responders and non-responders at baseline and after CSF diversion procedures.

Methods

Studies Selection

This review was performed according to PRISMA guidelines[7] and registered in PROSPERO (CRD42022301725). We searched the MEDLINE (https://pubmed.ncbi.nlm.nih.gov) and EMBASE (https://www.embase.com) database for studies in English published until December 2020 using the following search terms: "*normal pressure hydrocephalus" AND "gait analysis*" OR "*gait assessment*" *OR* "*quantitative gait*"; "*gait analysis*" AND "*tap test*" OR "*ventricular shunt*" OR "*lumbar peritoneal shunt*". Two independent reviewers (AM and MP) screened the abstracts to determine whether a full-text review should be performed. Duplicated articles, review articles, or articles using non-original data were excluded, but their bibliographies were reviewed to ensure additional articles were not missed. Data were extracted and double-checked by the two independent reviewers. Disagreements between the reviewers were resolved after discussion with other study authors until a consensus was reached.

Studies enrolling a cohort of iNPH patients (ie, fulfillment of iNPH available diagnostic criteria at the time of the study[8–14]/supportive clinical and radiological features and absence of clear causes of secondary NPH) and providing at least an objective gait measure with a sample size of at least 10 participants were selected. Only studies using instrumented system of gait assessment as optokinetic systems, motion sensors, or computerized gait mat were taken into account for the objective assessment.

Data Extraction

The following key data were extracted from the identified paper: iNPH diagnostic criteria, CSF diversion procedure, responsiveness criteria, time point of instrumental gait assessment, type of gait analysis, and gait parameters (Table S1). Other data included: demographic and clinical characteristics of iNPH patients (eg, number of patients, age, sex, disease duration), clinical or objective assessment, CSF diversion procedures (TT, CSS), time of the assessment post-TT (h), demographic and clinical characteristics of iNPH responder or non-responder to TT, time of the assessment post-CSS (weeks), features of patients that underwent CSS and their outcome, demographic and clinical characteristics of healthy controls. No data accounting for different CSS techniques–that is, endoscopic third ventriculostomy (ETV), lumbo-peritoneal shunt (LPS), ventriculo-atrial shunt (VAS), and ventriculo-peritoneal shunt (VPS)–were reported.

Studies varied substantially in the time when the gait analysis was performed after TT or CSS, and some also included multiple assessments (for example at 3, 6, 24, 72 hr from TT or 1, 4, 12 weeks from CSS). Irrespective of how much time elapsed after the procedure, we considered only one time point, selecting the one showing the best performance based on gait velocity. Numerous gait parameters during the assessment were analyzed and the most frequently reported parameters were included: velocity (m/s), cadence (steps/minute), step length (m), stride length (m), double limb support time (DLS, % of gait cycle). We also included the gait analysis results of age and sex-matched healthy controls, when available.

Patients were categorized into five subgroups according to responsiveness criteria of each study: TT responders (TT-R), CSS responders (CSS-R), TT non-responders (TT-NR), CSS non-responders (CSS-NR), and patients not classified in terms of their responsiveness to diversion procedures (TT/CSS-NC). Patients were also categorized as responders (R), composed by TT-R and CSS-R subgroups, and non-responder (NR), composed by TT-NR and CSS-NR subgroups. Patients were categorized in specific subgroups only if original papers provided separate data for these patients, otherwise they were categorized as TT/CSS-NC, even when the number of responder or non-responder was reported.

Quality Assessment

The Newcastle Ottawa Quality Assessment Scale (NOS) was used to assess the quality of the included studies by two independent reviewers. The NOS follows standard rules of study's reproducibility such as selection criteria, measures of comparability, outcomes used and rate of follow up over time.[15]Any differences between NOS results were discussed until a consensus was reached. A score inferior to 5 was considered poor quality, between 5 and 6 was considered fair quality, >6 was considered good quality.

In the studies selected for metanalysis, controls consisted of groups of individuals representing a different population from iNPH, mainly healthy controls and disease controls (i.e., progressive

supranuclear palsy, Parkinson's disease) who did not perform any diversion procedures (TT and/or CSS).

Statistical Methods

Demographic and clinical data were analyzed for the general population and subgroups whenever reported. To estimate the accuracy of specific gait variables, a meta-analysis was conducted for each variable reported in two or more studies. The analysis was based on subgroups to minimize heterogeneity. Heterogeneity was assessed using Cochran's Q Test and I^2 statistic tests.[16] I^2 values <50% are considered low, 50–75% moderate, and >75% high. A Q $P < 0.1$ or $I^2 \geq 50\%$ was considered significant heterogeneity. Potential sources of heterogeneity were explored with meta-regression analysis. The assessment of publication bias was performed only when 10 or more studies where available for meta-analysis by generating multiple funnel plots for the most frequently reported gait condition, excluding outliers.

Subgroup data was initially described in terms of means and standard errors for each outcome at different time points. Subsequently, the Comprehensive Meta-Analysis (Biostat Inc., Englewood, NJ, USA) software was used to analyze the effect size as means difference, or Hedges' g when the means difference was not available. A random-effects model was selected over a fixed-effect model to account for variability between studies which can likely be explained by factors other than sampling error. Other analyses included compared differences within the same subgroup and between each subgroup versus healthy controls at different time points. Values expressed as mean or percentage difference were taken into account. Data expressed as medians and ranges were excluded from the analysis. In order to lessen the impact of type α error, a more conservative P-value <0.01 was considered statistically significant.

Finally, a meta-regression analysis comparing improvement in gait velocity for each sample at different hours from TT was performed with curve fitting in MATLAB (The MathWorks Inc.,

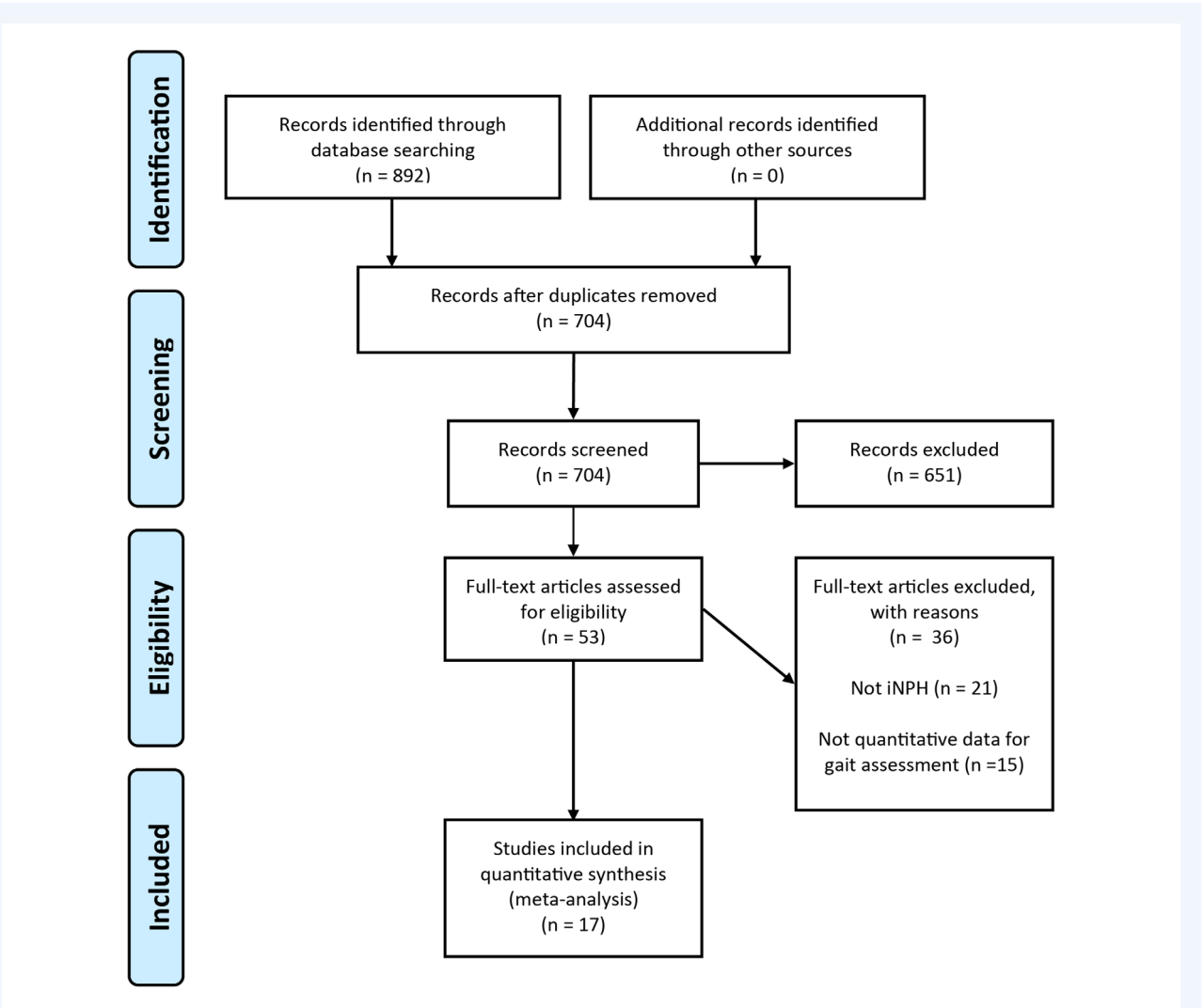

FIG 1. Flowchart of the initial literature search and extraction of studies meeting the inclusion criteria.

TABLE 1 *Summary of studies included in the meta-analysis*

Author, year	Study design	iNPH subgroups	iNPH (N)	Diversion Procedure	Outcome	Quality Assessment
Stolze et al 2001[17]	Case control	TT/CSS-NC	11	TT	Gait velocity Stride length DLS	Good
Armand et al 2011[18]	Prospective cohort	TT/CSS-NC	18	TT	Gait velocity Cadence Stride length	Poor
Agostini et al 2015	Prospective cohort	TT/CSS-NC	41	TT	Gait velocity DLS	Good
Schniepp et al 2017[19]	Prospective cohort	TT/CSS-NC (TT-R)*	24 (10)	TT	Gait velocity	Poor
Allali et al 2017	Prospective cohort	TT/CSS- NC (TT-R)*	68 (27)	TT/CSS	Gait velocity	Good
Backlund et al 2017	Case control	TT/CSS-NC	31	TT	Gait velocity	Good
Wolfsegger et al 2017[20]	Prospective cohort	TT/CSS-NC	11	TT	Gait velocity Stride length DLS	Good
Panciani et al 2018[2]	Prospective cohort	CSS-R CSS-NR	35 17	TT/CSS	Gait velocity Cadence Stride length DLS	Good
Chen et al 2018[21]	Cross-sectional	TT/CSS-NC	18	CSS	Gait velocity Cadence Step length DLS	Fair
Kitade et al 2018[22]	Prospective cohort	TT-R	12	TT	Gait velocity Cadence Step length	Poor
Nikaido et al 2018[23]	Prospective cohort	TT-R	23	TT	Gait velocity	Good
Selge et al 2018[24]	Cross-sectional	TT/CSS-NC	27	n/a	Gait velocity Cadence Stride length	Good
Colella et al 2019[3]	Case control	TT/CSS-NC	84	n/a	Gait velocity Cadence Stride length DLS	Poor

(Continues)

TABLE 1 *Continued*

Author, year	Study design	iNPH subgroups	iNPH (N)	Diversion Procedure	Outcome	Quality Assessment
Giannini et al 2019[6]	Prospective cohort	TT-R	35	n/a	Gait velocity Cadence Step length Stride length	Poor
Song et al 2019[25]	Prospective cohort	TT-R	28	TT/CSS	Gait velocity Cadence Stride length Step length	Poor
Lim et al 2019[26]	Prospective cohort	TT-R	23	TT	Gait velocity Cadence Stride length DLS	Good
Wolfsegger et al 2021[27]	Case control	TT-R TT-NR	10 11	TT/CSS	Gait velocity Step length	Fair

Note: Subgroups represented in parenthesis are part of the main iNPH subgroup for that article.
Abbreviations: CSS, cerebral spinal fluid shunt surgery; CSS-NR, cerebral spinal fluid shunt surgery non responders; CSS-R, cerebral spinal fluid shunt surgery responders; DLS, double limb support; iNPH, idiopathic normal pressure hydrocephalus; n/a, not applicable; N, number; TT/CSS-NC, patients not classified in terms of their responsiveness to tap test/cerebral spinal fluid shunt surgery; TT, tap test; TT-NR, tap test non responders; TT-R, tap test responders.
*Original articles providing separate data for responders only in the assessments after procedures.

Natick, MA, USA) using a smoothing spline model; weights were accounted as inverse of variance, differential gait velocity was considered as difference in means, when more time points were reported for the same subgroup, all of them were included in the analysis, to evidence the time evolution of gait velocity POST-TT. We assumed that at the origin of regression (time zero from tap test) there was no difference in gait velocity.

Results

Among the 892 articles identified through database search, 53 studies were initially selected. After a careful evaluation, a final list of 17 articles was considered eligible for the quantitative synthesis (Fig. 1, Table 1). The entire patient population consists of 527 patients (mean age of 74.8 ± 0.8, 37.6% female). The other clinical and demographic data of the different populations are presented in Table S2. Data from TT-NR,[27] CSS-R[2] and CSS-NR[2] were provided for each group only in one study, and therefore were not reported in online Table S2.

The quality assessment revealed an overall heterogeneity across studies included in this meta-analysis. The main bias encountered was that many studies provided incomplete data about subgroups differences, limiting the evidence for NR patients. Moreover, most of the studies performed only one assessment of gait response POST-TT or POST-CSS selecting arbitrary time intervals from diversion procedure, thus resulting in a great heterogeneity. Finally, few studies investigated gait improvement after CSS underlying the lack of longitudinal data to monitor improvement over time.

Entire iNPH Sample

When considering the entire iNPH sample, a significant response in each selected gait parameter was observed POST-TT and POST-CSS. Moreover, a significant difference could be appreciated comparing POST-TT to POST-CSS for each meta-analysis outcome (Table S3, Fig. 2A). Healthy controls performed consistently better than iNPH patients at baseline in each meta-analysis outcome and this difference retained statistical significance even POST-TT and POST-CSS (Table S4, Fig. 2B). However, heterogeneity between the studies was shown to be high for each outcome.

Subgroups Analyses

Meta-analyzable data were available only for TT-R and TT/CSS-NC. Patients grouped as TT-NR, CSS-R, CSS-NR were only available from single studies, so no meta-analysis could be performed for these specific subgroups. Table S5 shows the meta-analysis data for each subgroup at the three different time points.

TT-R improved significantly POST-TT and even more POST-CSS in each meta-analysis outcome (Table S6, Fig. 3). At baseline, their gait parameters were significantly worse than healthy controls and remained so POST-TT and POST-CSS

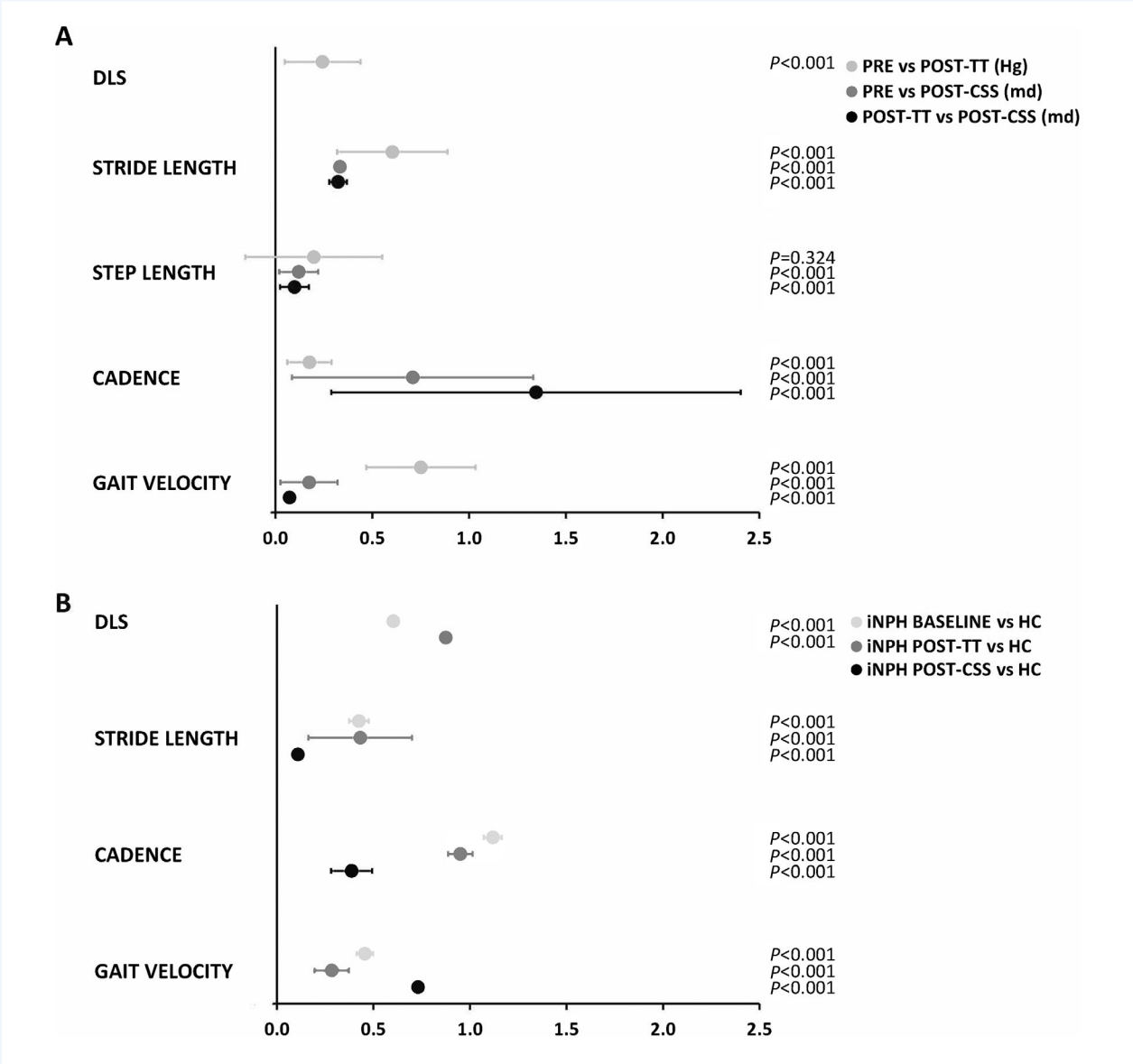

FIG 2. (A) Differential values between the three time points for all the iNPH patients gathered by this review. Data are expressed as means difference (*P*-value) or Hedges' g (*P*-value), 99% CI. Values of cadence and of step length at PRE vs POS-TT condition have been normalized (1:10) for graphic representation purposes. (B) Comparison between all the iNPH patients gathered by this review and healthy controls. Data are expressed as means difference (*P*-value), 99% CI. Values of cadence have been normalized (1:10) for graphic representation purposes. DLS: double limb support; md: means difference; HC: Healthy controls; Hg: Hedges' g; iNPH: idiopathic normal pressure hydrocephalus; POST-CSS: gait analysis acquired after CSF shunt surgery; POST-TT: gait analysis acquired after tap test; PRE: gait analysis acquired at baseline.

(Table S7, Fig. 4A,B). TT/CSS-NC improved significantly POST-TT in the available data: gait velocity, stride length, and DLS (Table S6, Fig. 3). TT/CSS-NC further improved POST-CSS in terms of gait velocity, the only available meta-analyzable outcome (Table S6, Fig. 3). In spite of these improvements, the TT/CSS-NC subgroup was significantly worse than healthy controls at baseline, POST-TT (gait velocity, stride length and DLS), and POST-CSS (gait velocity) (Table S7).

When lumping CSS-R and TT-R into the category of R, gait velocity improved consistently after TT (Hedges' g: 0.20, $P < 0.0001$), unlike NR (TT-NR and CSS-NR), whose values PRE and POST-TT did not differ ($P = 0.375$; Table S8).

Meta-Regression of Gait Velocity POST-TT at Different Time Points

Eleven different subgroups from 10 different studies were included in the meta-regression. The curve fitting regression depicted in Figure 5 follows a smoothing spline model, showing

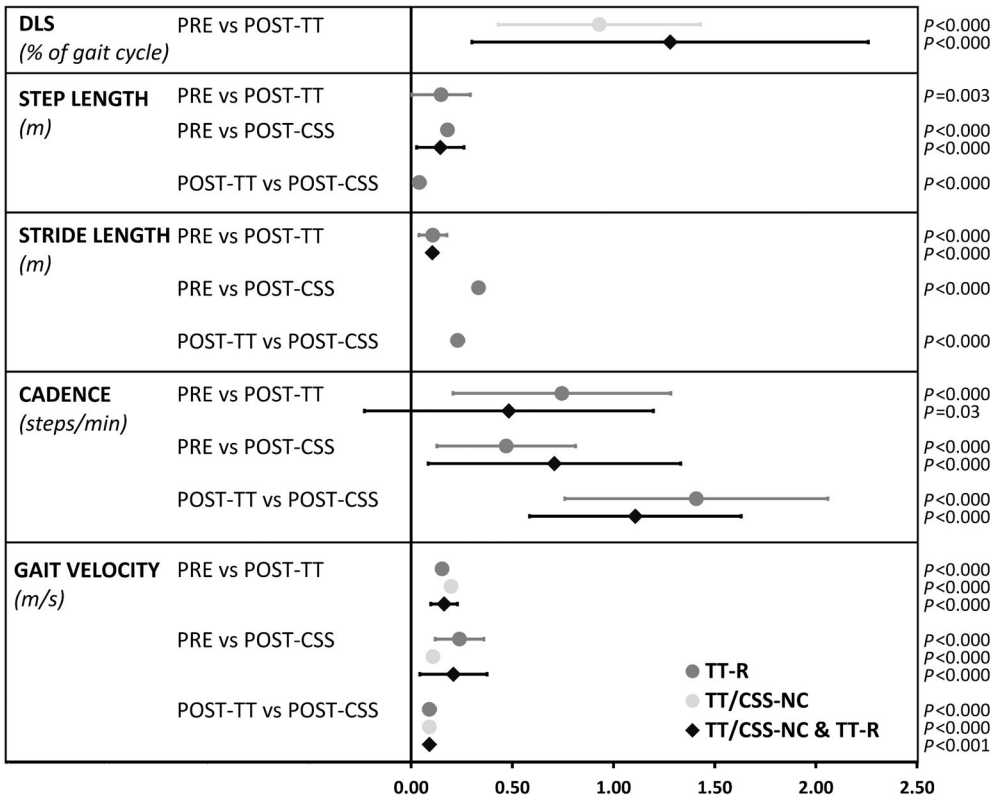

FIG 3. Differential values at the three time points for iNPH subgroups. Data are expressed as means difference (p-value), 99% CI. Values for cadence have been normalized (1:10) for graphic image purposes. DLS: double limb support; POST-CSS: gait analysis acquired after CSF shunt surgery; POST-TT: gait analysis acquired after tap test; PRE: gait analysis acquired at baseline; TT/CSS-NC: patients not classified in terms of their responsiveness to tap test/cerebral spinal fluid shunt surgery; TT-R: tap test responders.

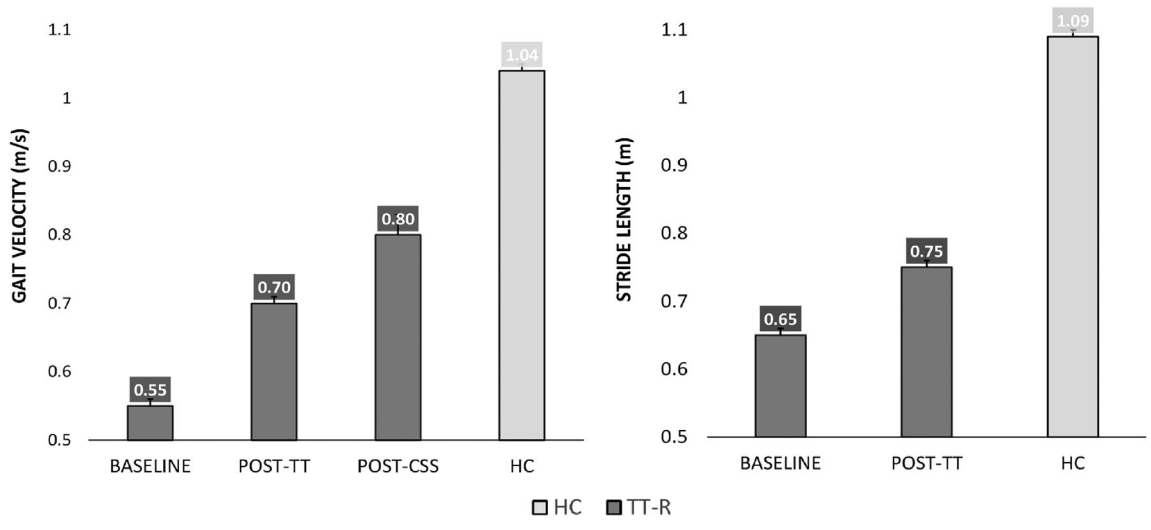

FIG 4. Comparison of gait velocity (left) and stride length (right) between TT-R at different time points and healthy controls. Data are expressed as means and standard error. POST-CSS: gait analysis acquired after CSF shunt surgery; POST-TT: gait analysis acquired after tap test; PRE: gait analysis acquired at baseline; TT-R: tap test responder.

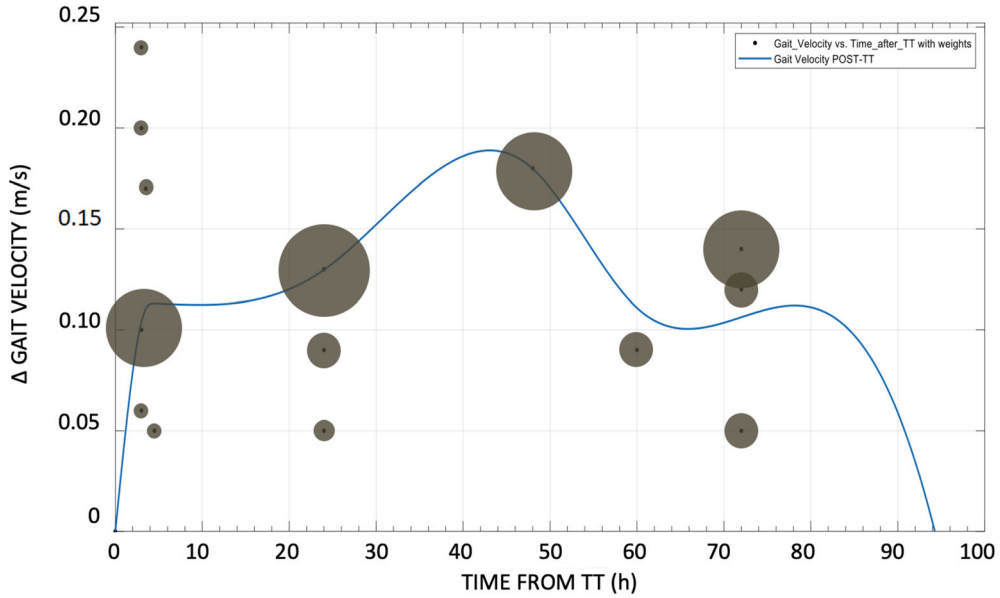

FIG 5. (A). A meta-regression analysis comparing improvement in gait velocity for each sample at different hours from TT (MATLAB, The MathWorks Inc, Natick, MA, USA). Data were obtained as difference in means between POST-TT and PRE assessment for each study subgroup (represented as black dots), weights were accounted as inverse of variance (represented as gray proportional bubbles). No difference in gait velocity was assumed at the origin of regression (time zero from tap test). Curve fitting regression: smoothing spline model (smoothing parameter: 0.02, goodness of fit: SSE: 0.050, R-square: 1, Adjusted R-square: 1, RMSE: 0.071, goodness of validation: SSE: 0.050, RMSE: 0.056).

a stable velocity variation maximum around 24–48 hr after TT and progressively return to baseline in 90–100 hr. Due to a lack of consistent data, a similar analysis could not be obtained for velocity variation after CSS. Regression for velocity variation using age as a predictor did not depict any linear association, while a similar analysis for symptom duration was not possible because of the lack of data.

Conclusions

This meta-analysis gathered gait analysis data from 527 iNPH patients and focused on five objective gait measures (velocity, cadence, step length, stride length, and double limb support) that can be used in the clinical setting to characterize the gait features of these patients, as compared to healthy controls or before and after CSF-diversion procedures. The main findings from this work indicate that (1) as a whole, the iNPH cohort and the TT-R subgroup improved in each gait measure after TT and the improvement was even greater after CSS; (2) gait analysis allows to differentiate iNPH from healthy controls; (3) we identified different sources of heterogeneity in the published literature: few articles reported separately data regarding TT-NR and CSS-NR; the time of gait reassessment after TT and after CSS were not standardized across different studies, (4) finally, a meta-regression analysis revealed that improvement after TT reached its plateau around 24–48 hr after procedure.

In line with the above-mentioned results, our meta-analysis supports the use of gait analysis as an instrumental tool to identify patient's responsiveness to TT procedure and to differentiate iNPH from healthy controls. Interestingly, a significant improvement was evidenced POST-CSS compared to POST-TT, reinforcing the idea that CSS exerts a more profound effect on iNPH pathophysiology due to the prolonged CSF drainage.[28] Notably, despite the improvement after TT or CSS, iNPH gait never completely normalized, as shown by the comparison with healthy controls at different time points. This observation supports the notion that the CSF dynamic alteration typical of iNPH also leads to irreversible damage, potentially promoting a neurodegenerative process.[29]

In order to mitigate the clinical and statistical heterogeneity of the entire iNPH sample, we reported data from the different subgroups of responders and non-responders. As expected, TT-R patients improved POST-TT and POST-CSS in each selected gait outcome. The improvement after CSS was again greater than after TT, reinforcing the idea that the magnitude of the response to CSS may not be completely predicted by TT. On the other hand–and in keeping with existing data,[30] a negative response to TT has a low negative predictive value and does not reliably make iNPH patients ineligible for shunting.

Distinguishing responders from non-responders should represent one of the primary goals of iNPH research, as the candidate selection for the shunt procedure is the most important management decision and remains imperfect. Therefore, the limited

number of articles reporting data about TT-NR and CSS-NR highlights the need for a radical change in longitudinal NPH studies. To overcome these limitations, we lumped the data from TT-R and CCS-R and compared this with the data from TT-NR lumped with CSS-NR. Not surprisingly, gait velocity, the only available outcome measure, did not show any significant difference between pre and post-TT for the latter group in contrast to responders. This finding supports the utility of the TT procedure in selecting CSS candidates, although limitations remain.

Data presented by our subgroup of TT-R patients demonstrate which kinematic gait features (at baseline and POST-TT) are likely to improve with CSS. In particular, gait velocity of 0.55 ± 0.01 m/s (extracted from 109 patients) with an improvement of 0.155 m/s after TT (120 patients) might be characteristic of this subgroup. In fact, data coming from a single study of 10 TT-NR patients show higher gait velocity at baseline (0.75 ± 0.08 m/s) with a poor improvement after TT of only 0.06 m/s. These differences might support the utility of quantitative gait analysis as a tool to discriminate between responders and non-responders. Alternatively, it might be hypothesized that iNPH patients with a better gait performance at baseline may fail to show improvement after TT due to a ceiling effect. Another important factor biasing the individual response to TT is represented by disease duration at the time of TT. Indeed, a longer disease duration might be associated with a poorer response after TT even if one study argues against this theory.[31] Unfortunately, studies collected in our meta-analysis did not provide enough information to support or confute this hypothesis.

Beyond the need of standardizing TT responsiveness criteria, studies revised by our meta-analysis revealed a profound heterogeneity regarding the time of assessment after the lumbar puncture, ranging from 2 to 72 hr. Some studies proposed also a repetition of POST-TT assessment at different times. Data from literature suggest that the best moment to appreciate an improvement in gait features is within 24 hr after TT.[32] However, our meta-regression analysis reveals that the effect of TT reaches a plateau after 24–48 hr, thus representing the best moment to assess gait improvement, in keeping with personal observations. Interestingly, our meta-regression also identified a progressive reduction of differential gait velocity, with a return to baseline conditions in 90–100 hr after TT. It could be argued that such pattern is susceptible to single individual performance, possibly meaning that each subject has a different latency of response. Thus, the common practice of assessing TT responses on the same day might carry the risk of missing CSS candidates. In this regard, our findings indicate that the best moment to assess gait improvement is within 24-48 hr after TT.

Data from our study demonstrate that gait analysis is a valid tool to differentiate iNPH patients from healthy controls. However, discriminating iNPH patients from other hypokinetic gait disorders may be very challenging, especially when MRI demonstrates ventriculomegaly. Unfortunately, there was insufficient data in our meta-analysis to compare objective gait data from iNPH patients with other diseases (ie, progressive supranuclear palsy, Parkinson's disease, myelopathy, and metabolic diseases).[17,24,33] Nevertheless, each of these studies demonstrated how objective gait analysis may be useful in the differential diagnosis of iNPH, encouraging further studies in this direction. In addition, one of these articles focused on quantitative gait assessment during dual-task, thus providing evidence for a possible role of this task in the diagnostic process of iNPH. The study showed an improvement in gait velocity of iNPH patients during a dual motor task, in contrast to patients with progressive supranuclear palsy, whose gait worsened. According to the authors, this improvement may be explained by increased activity of the prefrontal cortex, which partly compensates for the loss of callosal interhemispheric connections in iNPH.[24]

Our meta-analysis carries several limitations, partly discussed in the previous paragraphs. The demographic analysis was conducted over the general population and subgroups, but no precise data are available for each outcome at different time points for each subgroup, preventing us from excluding specific confounding factors for each analysis. Moreover, the clinical features were not consistently reported across the different papers, thus limiting our ability to characterize the different patient groups. Many articles presented gait PRE, POST-TT, and POST-CSS data, without specifying if those values referred to a population of responders or non-responders, resulting in the heterogeneous group of TT/CSS-NR. Additionally, in some studies, not all included patients underwent a CSF diversion procedure, or TT followed by CSF shunt. Furthermore, an evident similarity was observed between the outcomes of TT/CSS-NC and TT-R likely resulting from the fact that the former group is composed mainly of TT-R. Alternatively, these studies only enrolled selected patients with a greater chance to improve after TT or CSS, such as patients without evidence of neurodegeneration, that is dementia, younger age, or disproportionately enlarged subarachnoid-space hydrocephalus.[20] Unfortunately, data for TT-NR and CSS-NR were provided only by single studies making it impossible to perform a meta-analysis of non-responders, which may indicate a publication bias.

Thus, for some studies, there was only data available at baseline or after a single CSF diversion procedure.

Moreover, few studies reported more than one assessment for the same time point, especially regarding POST-TT or POST-CSS. In the meta-analysis, we selected the assessments performed at the best gait velocity for the purpose of estimating the full potential of gait improvement after the procedures. Conversely, in order to explore the time evolution of gait velocity POST-TT, our meta-regression analysis included each assessment following the procedure. There was also insufficient data collected to analyze and compare the outcomes resulting from different CSS techniques (ie, ETV, LPS, VAS, and VPS). Another important limitation is the lack of uniform criteria used to label patients as responders or non-responders. Of the few articles identifying a population of TT-R, and the only one identifying a population of CSS-R,[2] used arbitrary criteria and utilized different clinical scales at different time points. Finally, no data coming from patients undergoing external lumbar drainage was found most likely reflecting the relatively infrequent use of this more invasive test requiring hospital admission.

In conclusion, this meta-analysis found that gait analysis is a useful method to differentiate iNPH patients from healthy

controls and can help identify patients who are responsive to CSF diversion procedures. Longitudinal studies focusing on a single patient's performance over time after CSF diversion procedures are required to determine whether there are individual factors, aside from timing assessment after the intervention, which explain the heterogeneity of responses to CSF removal. These studies will also help define the impact of disease duration on the reversibility of the symptoms.

Finally, considering that most studies were poorly designed, there is an urgent need for standardized reporting method in iNPH research that includes criteria of responsiveness, specific gait parameters, and timeframe of assessment.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique.

M.P.: 1A, 1B, 1C, 2A, 2B, 2C, 3A
A.M.: 1A, 1B, 1C, 2A, 2B, 2C, 3A
B.B.: 2C, 3B
R.R.: 2C, 3B
A.F.: 1A, 1B, 3B.

Disclosures

Ethical Compliance Statement: The authors confirm that the approval of an institutional review board and patient consent were not required for this work. We confirm that no informed consent was required for this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Data Availability Statement

Qualified Investigators may request access to data including raw extraction datasets, analysis-ready datasets, PRISMA Check List, Quality assessment tables, Publication Bias assessment dataset and graphs, Heterogeneity assessment dataset, statistical analysis plan. ■

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Supporting Information

Supporting information may be found in the online version of this article.

Table S1. Data extracted for the meta-analysis. CSF: cerebrospinal fluid; iNPH idiopathic NPH; NPH: normal pressure hydrocephalus. POST-TT: gait analysis acquired after tap test; POST-CSS: gait analysis acquired after CSF shunt surgery; PRE: gait analysis acquired at baseline.

Table S2. Demographic and clinical data. Values are mean ± SE (number of available patients if less than indicated in the first row) or N (%).* Some original articles reported the number of responder/non-responder without providing separate data for these patients, that could not be categorized in subgroups. Abbreviations: iNPH: idiopathic Normal Pressure Hydrocephalus; POST-CSS: gait analysis acquired after cerebral spinal fluid shunt surgery; POST-TT: gait analysis acquired after tap test; TT/CSS-NC: patients not classified in terms of their responsiveness to tap test/cerebral spinal fluid shunt surgery; TT-R: Tap test responders.

Table S3. Comparisons of the iNPH patients gait parameters. Data are expressed as means difference (*P*-value) or Hedges' g (*P*-value). Abbreviations: DLS: double limb support, iNPH: idiopathic normal pressure hydrocephalus; NA: not available; POST-CSS: gait analysis acquired after CSF shunt surgery; POST-TT: gait analysis acquired after tap test; PRE: gait analysis acquired at baseline.

Table S4. Comparisons between all the iNPH patients and healthy controls. Data are expressed as mean difference (*P*-value). Values derived from one study[1]: Chen et al., 2018. DLS: double limb support; POST-CSS: gait analysis acquired after CSF shunt surgery; POST-TT: gait analysis acquired after tap test; PRE: gait analysis acquired at baseline.

Table S5. Meta-analyses of the gait parameters. Data are expressed as mean ± standard error (n of the sample, heterogeneity I^2). Values derived from one study[1]: Lim et al., 2019[2]; Kitade et al., 2018[3]; Wolfsegger et al., 2020. Abbreviations: DLS: double limb support; POST-CSS: gait analysis acquired after CSF shunt surgery; POST-TT: gait analysis acquired after tap test; PRE: gait analysis acquired at baseline; TT/CSS-NC: Tap test/cerebral spinal fluid shunt surgery not classified; TT-R: tap test responders.

Table S6. Within subgroups comparisons at different time points. Data are expressed as means difference (p-value). Values derived from one study[1]: Armand et al., 2011[2]; Chen et al., 2018[3]; Lim et al., 2019. DLS: double limb support; POST: acquisition after diversion procedure; POST-TT: gait analysis acquired after tap test; POST-CSS: gait analysis acquired after CSF shunt surgery; PRE: gait analysis acquired at baseline; TT/CSS-NC: Tap test/cerebral spinal fluid shunt surgery not classified; TT-R: Tap test responders.

Table S7. iNPH subgroups at different time points vs healthy controls. Data are expressed as means difference (*P*-value). Values derived from one study[1]: Lim et al., 2019[2]; Kitade et al., 2018[3]; Chen et al., 2018. DLS: double limb support NA: not available; POST-CSS: gait analysis acquired after CSF shunt surgery; POST-TT: gait analysis acquired after tap test; PRE: gait analysis acquired at baseline; TT/CSS-NC: Tap test/ cerebral spinal fluid shunt surgery not classified; TT-R: Tap test responders.

Table S8. Responder and non-Responder data. Data are expressed as Hedges' g (*P*-value). NR: non-Responders; POST-TT: gait analysis acquired after tap test; PRE: gait analysis acquired at baseline; R: responders