

ORIGINAL ARTICLE

Mobile digital gait analysis captures effects of botulinum toxin in hereditary spastic paraplegia

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Abstract

Background and purpose: Hereditary spastic paraplegias (HSPs) comprise a group of inherited neurodegenerative disorders characterized by progressive spasticity and weakness. Botulinum toxin has been approved for lower limb spasticity following stroke and cerebral palsy, but its effects in HSPs remain underexplored. We aimed to characterize the effects of botulinum toxin on clinical, gait, and patient-reported outcomes in HSP patients and explore the potential of mobile digital gait analysis to monitor treatment effects and predict treatment response.

Methods: We conducted a prospective, observational, multicenter study involving ambulatory HSP patients treated with botulinum toxin tailored to individual goals. Comparing data at baseline, after 1 month, and after 3 months, treatment response was assessed using clinical parameters, goal attainment scaling, and mobile digital gait analysis. Machine learning algorithms were used for predicting individual goal attainment based on baseline parameters.

Results: A total of 56 patients were enrolled. Despite the heterogeneity of treatment goals and targeted muscles, botulinum toxin led to a significant improvement in specific clinical parameters and an improvement in specific gait characteristics, peaking at the 1-month and declining by the 3-month follow-up. Significant correlations were identified between gait parameters and clinical scores. With a mean balanced accuracy of 66%,

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machine learning algorithms identified important denominators to predict treatment response.

Conclusions: Our study provides evidence supporting the beneficial effects of botulinum toxin in HSP when applied according to individual treatment goals. The use of mobile digital gait analysis and machine learning represents a novel approach for monitoring treatment effects and predicting treatment response.

KEYWORDS

botulinum toxin, gait analysis, lower extremity, muscle spasticity, spastic paraplegia, hereditary

INTRODUCTION

Hereditary spastic paraplegias (HSPs) encompass a group of rare, genetically heterogeneous neurological disorders, hallmarked by progressive spasticity and weakness in the lower limbs. The underlying pathology is a length-dependent degeneration of the corticospinal tracts and dorsal columns, with a wide range of age at onset, severity, and progression rate, which complicates diagnosis and treatment [1–3]. Despite substantial progress in elucidating the genetic basis and molecular mechanisms, effective disease-modifying interventions are lacking [4, 5].

Therefore, current treatment is purely symptomatic and aims to improve mobility and quality of life by reducing cramps, pain, and secondary complications such as falls and contractures. Botulinum neurotoxin (BoNT) was approved for the treatment of lower limb spasticity in patients with stroke, traumatic brain injury, and cerebral palsy [6].

Previous studies on BoNT in HSPs, however, were conducted on small cohorts with few genotypes, and there is a lack of objective treatment outcomes [7, 8]. Mobile gait analysis has been introduced to provide objective gait measures that might be more sensitive for capturing gait-related mobility in HSPs and other rare neurological diseases [9–11].

In this study, we sought to (i) investigate the effects of BoNT on clinical scores, patient-reported outcomes, and gait parameters obtained using a wearable gait analysis system in a multicenter setting; (ii) investigate the potential of digital gait parameters to reflect clinical response; and (iii) use machine learning models for the prediction of treatment response based upon baseline parameters. Hence, we strive to improve the understanding of BoNT treatment for HSP patients. Moreover, the use of wearables might pave the way for a more accurate and objective assessment of treatment response over time to reduce the number of subjects required for future clinical trials in rare movement disorders.

METHODS

Recruitment and inclusion criteria

The study design was multicenter, prospective, and observational. Between January 2020 and February 2022, patients were recruited at three different specialized HSP centers during regular clinic

visits (Department of Molecular Neurology at University Hospital Erlangen, Department of Neurology at University Hospital Essen, and the Center of Neurology at University Hospital Tübingen) as part of a European clinical consortium ([TreatHSP.net](https://www.treathsp.net)). Patients were recruited if (i) they had a clinical or genetic diagnosis of HSP, (ii) treatment with BoNT was performed, and (iii) they were able to walk at least 10m either with or without a walking aid. Patients were excluded if they exhibited any comorbidity that might significantly impact motor abilities. Each participant gave written informed consent, endorsed by the respective local ethics committees: Friedrich Alexander University Erlangen-Nuremberg (No. 166_18B and 347_17B), University of Essen (No. 19-8762-BO), and University of Tübingen (432/2019BO1 and 347/2019BO2). Patient characteristics at baseline are presented in [Table 1](#).

BoNT treatment

The indication for BoNT treatment, goal setting, BoNT type, and injection schemes were made on a clinical basis before study inclusion. Guided by ultrasound, BoNT injections were performed by board-certified neurologists experienced in BoNT treatment. All of the three BoNT formulations approved in Germany were utilized: abobotulinumtoxinA, incobotulinumtoxinA, and onabotulinumtoxinA. For each patient, the treatment regimen and respective dosage were determined individually, depending on the affected muscles and treatment goals ([Table 1](#)).

Clinical and gait assessment

The study protocol is depicted in [Table S1](#). All patients performed clinical and gait assessments at baseline (just before injection), after 1 month, and after 3 months for follow-up, including the Spastic Paraplegia Rating Scale (SPRS; ranging from 0 indicating no symptoms to 52) [12], and the modified Ashworth Scale (mAS; ranging from 0 to 4) [13] of the adductor, quadriceps, triceps surae, and tibialis posterior muscles. In a subset of patients ($n=49$), the Montreal Cognitive Assessment [14] was performed at baseline. A maximum of three treatment goals were defined together with each patient, following the principles specific, measurable, achievable, relevant, and time-bound. The Goal Attainment Scale (GAS)

TABLE 1 Patient demographic and clinical characteristics at baseline.

Age, years, mean $\pm$ SD	52.1 $\pm$ 11.1
Sex	Male, 25; female, 31
Disease duration, years, mean $\pm$ SD	20.4 $\pm$ 15.3
BoNT product and dosage	
AbobotulinumtoxinA	<i>n</i> = 17; mean dose = 621.2 IU
IncobotulinumtoxinA	<i>n</i> = 9; mean dose = 319.4 IU
OnabotulinumtoxinA	<i>n</i> = 30; mean dose = 326.4 IU
Treated muscles	
Triceps surae	<i>n</i> = 45, mean dose = 109.9 IU
Adductor	<i>n</i> = 32, mean dose = 133.5 IU
Flexor digitorum longus	<i>n</i> = 15, mean dose = 39.7 IU
Tibialis posterior	<i>n</i> = 20, mean dose = 64.4 IU
Flexor digitorum brevis	<i>n</i> = 4, mean dose = 40 IU
Extensor hallucis longus	<i>n</i> = 1, mean dose = 20 IU
Rectus femoris	<i>n</i> = 2, mean dose = 75 IU
Biceps femoris	<i>n</i> = 1, mean dose = 130 IU
Semitendinosus	<i>n</i> = 1, mean dose = 400 IU
Vastus medialis	<i>n</i> = 1, mean dose = 100 IU
Goal setting	
Improve gait stability	<i>n</i> = 44 (78.6%)
Improve gait speed	<i>n</i> = 34 (60.7%)
Reduce toe clawing	<i>n</i> = 12 (21.4%)
Reduce pain	<i>n</i> = 19 (33.9%)
Reduce muscle cramps	<i>n</i> = 20 (35.7%)
Genotype	
SPAST	<i>n</i> = 23
SPG7	<i>n</i> = 4
REEP1	<i>n</i> = 2
SPG11	<i>n</i> = 2
ABCD1	<i>n</i> = 2
ATL1	<i>n</i> = 1
CYP7B1	<i>n</i> = 1
GDAP1	<i>n</i> = 1
KIF1C	<i>n</i> = 1
KIF5A	<i>n</i> = 1
MT-ATP6	<i>n</i> = 1
TUBB4A	<i>n</i> = 1
RTN2	<i>n</i> = 1
Unknown	<i>n</i> = 15
Walking aid	
None	<i>n</i> = 33
Walking stick	<i>n</i> = 16

(Continues)

TABLE 1 (Continued)

Wheeled walker	<i>n</i> = 4
Functional electrical stimulation	<i>n</i> = 2
Assisting person	<i>n</i> = 1
Physiotherapy	
h/week, mean $\pm$ SD	1.8 $\pm$ 1.1

Abbreviation: BoNT, botulinum neurotoxin.

was evaluated at the 1-month follow-up visit [15, 16]. The score ranges from 0 to 4, with 0 indicating decline from baseline, 1 indicating no change or less than expected, 2 indicating expected response, 3 indicating somewhat more than expected, and 4 indicating much more than expected. For gait assessment, patients performed a standardized 4 $\times$ 10-m gait test, walking as fast as possible without increasing the risk of falling, at baseline and follow-up visits. During this task, the Mobile GaitLab system (Portables HealthCare Technologies, Erlangen, Germany) was used for acquiring gait data, where each patient was equipped with one inertial measurement unit (IMU) sensor at each foot attached to the shoes at the instep position. Each IMU consists of a triaxial accelerometer (range $\pm$ 8 g) and a triaxial gyroscope (range $\pm$ 2000°/s). The data were recorded at a sampling frequency of 102.4 Hz and transmitted to a tablet via Bluetooth. For analysis, data were segmented into single strides using a hidden Markov model-based algorithm validated for stride segmentation in HSP patients [17]. A graphical user interface was used for manually excluding turning strides [18]. Initiation and termination strides were excluded due to the substantial variability compared to the steady-state strides [9]. Stridewise gait parameters were extracted, and mean and variability (coefficient of variation [CV]) values of both feet were calculated for further analysis.

Patient-reported outcome measures collected at baseline and follow-up visits included the Falls Efficacy Scale International questionnaire (FES-I) [19] and the Short Form 12 questionnaire (SF-12; and its derived physical and mental component scores) [20].

Statistical analysis

Details on the statistical analysis are provided in the Supplemental Methods. Generalized linear mixed models were used to analyze the change of each parameter over the three time points with *time* as a fixed effect and *patient* as a random effect [21]. For pairwise comparison between time points, post hoc tests were performed using the “emmeans” R package [22]. Multiple comparisons were conservatively adjusted by the Bonferroni correction (α = 0.05). In case of missing data caused by missed follow-up visits or technical reasons (Table 2), all data from the respective time points were excluded. Correlation analyses were performed on individual changes between baseline and 1 month. Absolute differences were calculated for the clinical and patient-reported measures and relative changes for gait parameters [23]. Spearman rank correlations (ρ) were calculated at α = 0.05.

For the prediction of treatment response using baseline measures, we tested different supervised machine learning models (Supplemental Methods, Table S4) [24, 25]. Patients were considered to be responders if at least one of three GAS scores was ≥ 2 . Additionally, we defined "GAS-gait" as the maximum value of GAS for goals that were gait-related, for example, improving gait speed or enhancing gait stability. Similarly, a patient was considered a responder to gait-related goals if GAS-gait was ≥ 2 .

RESULTS

Recruitment and patient characteristics

The baseline characteristics of the study cohort are listed in Table 1. A total of 82 HSP patients treated with BoNT (either for the first time or for recurrent treatment) were screened at the three study centers. Fifty-six patients were enrolled in the study (21 patients at University Hospital Erlangen, 22 at University Hospital Essen, and 13 at University Hospital Tübingen). The remaining 26 patients were ineligible because of inability to walk or refusal of consent.

SPAST-related HSP was the most frequent genotype, but many different additional genotypes as well as unresolved HSP cases were included. BoNT formulations were used at doses consistent with their different bioequivalence [26]. The majority of treatment goals were related to gait stability and gait speed, and additional goals addressed discomfort due to muscle pain, muscle cramps, or toe clawing. Less than half of the enrolled patients were regularly using a walking aid. In 34 patients, BoNT had been used before, at a median of 4.5 (range = 1–41) injection cycles. In six patients, measurements were performed over two injection intervals, and for one patient over three injection intervals, amounting to 64 treatment cycles that were analyzed. In all participants, the frequency of physiotherapy and dose of antispastic oral treatment (if applicable) remained unchanged during follow-up.

Clinical and gait improvement 1 month after BoNT treatment

We first characterized the changes in clinical measures, patient-reported outcomes, and gait parameters, comparing baseline,

TABLE 2 Change of clinical, gait, and patient-reported measures with time and *p*-values of the post hoc comparisons of these measures between the three visits.

Parameters	Baseline		1-month follow-up		3-month follow-up		<i>p</i> (baseline vs. 1 month)	<i>p</i> (baseline vs. 3 months)	<i>p</i> (1 month vs. 3 months)
	<i>n</i>	Mean ± SD	<i>n</i>	Mean ± SD	<i>n</i>	Mean ± SD			
Clinical parameters									
mAS adductors	64	1.6 ± 0.9	64	1.2 ± 0.8***	42	1.5 ± 0.8 [†]	0.0005***	0.7	0.03 [†]
mAS quadriceps	64	1.5 ± 0.7	64	1.5 ± 0.7	42	1.6 ± 0.8	1.0	0.4	0.06
mAS triceps surae	64	1.7 ± 0.8	64	1.1 ± 0.7***	42	1.3 ± 0.8	0.0001***	0.1	0.3
mAS tibialis posterior	64	1.3 ± 0.7	64	1.0 ± 0.6*	42	1.2 ± 0.7	0.01*	1.0	0.2
SPRS (total score)	64	18.2 ± 6.8	64	16.5 ± 6.6***	42	17.6 ± 6.6 ^{†††}	0.0002***	1.0	<0.0001 ^{†††}
Patient-reported parameters									
FES-I	58	34.1 ± 12.2	51	34.2 ± 12.6	20	37.9 ± 13.9	1.0	1.0	1.0
SF-12 mental component	58	49.8 ± 13.3	50	49.3 ± 13.6	40	51.4 ± 12.3	1.0	1.0	1.0
SF-12 physical component	58	30.6 ± 14.1	50	33.5 ± 12.6	40	32.6 ± 13.5	0.4	1.0	1.0
Gait parameters									
Gait speed, m/s	64	0.7 ± 0.3	64	0.8 ± 0.3	30	0.7 ± 0.2	0.3	1.0	1.0
Stride time, s, mean	59	1.5 ± 0.5	59	1.4 ± 0.4	34	1.4 ± 0.5	0.7	1.0	0.2
Stance time, s, mean	59	1.0 ± 0.4	59	1.0 ± 0.3	34	1.0 ± 0.4	0.5	1.0	0.2
Relative swing duration	59	0.3 ± 0.0	59	0.3 ± 0.0	34	0.3 ± 0.0	0.2	1.0	0.9
Stride time CV	59	0.06 ± 0.03	59	0.05 ± 0.02	34	0.06 ± 0.0	0.4	0.9	0.08
Stance time CV	59	0.07 ± 0.03	59	0.07 ± 0.03	34	0.08 ± 0.0	0.6	0.5	0.06
Relative swing duration CV	59	0.08 ± 0.06	59	0.07 ± 0.04	34	0.09 ± 0.05 ^{††}	0.2	0.5	0.007 ^{††}

Note: Mean values $\pm$ SD are given for clinical, patient-reported, and gait parameters at the three study time points. Probability values were calculated according to a generalized linear mixed model and adjusted for multiple testing. Significant *p*-values are indicated in bold: **p* < 0.05, ****p* < 0.001 comparing baseline to 1-month follow-up; [†]*p* < 0.05, ^{††}*p* < 0.01, ^{†††}*p* < 0.001 comparing 1-month to 3-month follow-up. There were no significant differences comparing baseline to 3-month follow-up. Probability values are adjusted with Bonferroni correction).

Abbreviations: CV, coefficient of variation; FES-I, Falls Efficacy Scale International; mAS, modified Ashworth Scale; SF-12, Short Form 12 questionnaire; SPRS, Spastic Paraplegia Rating Scale.

1-month, and 3-month time points in a mixed-effects model. There was a significant improvement in spasticity of the adductors, triceps surae, and tibialis posterior muscles as well as for SPRS scores comparing baseline to 1-month follow-up (Table 2, Figure 1). When comparing the 1-month to the 3-month time point, spasticity of the adductors and SPRS significantly worsened (Table 2, Figure 1). No significant differences were present comparing baseline and 3-month follow-up, compatible with the expected wearing off of the effects of BoNT 3months after treatment. Patient-reported parameters did not show significant changes over time (Table 2). Regarding goal attainment, the mean GAS ($\pm$ SD) of all patients was 1.4 ($\pm$ 0.9), and 37 of 56 (66%) patients reported a positive outcome at least as expected (GAS $\geq$ 2), indicating an overall positive treatment response. Simultaneously, 19 of 56 (34%) patients reported an outcome of “worse than baseline” ($n=9$) or “same as baseline/less than expected” ($n=10$), highlighting the need to predict and objectively record treatment response.

For gait analysis data, we extracted gait speed, stride time, stance time, and relative swing duration as well as their CVs. There were no significant changes in gait parameters after 1 month, but there was a significant worsening in relative swing duration CV values when comparing 1-month to 3-month follow-up (Table 2).

Furthermore, the number of previous treatment cycles had a significant effect on a subset of gait and clinical parameters including SPRS, walking speed, stance time, and stride time.

Gait parameters reflect individual treatment response

Given the heterogeneity concerning our cohort and the individual treatment responses, we next addressed whether mobile gait parameters capture clinical and patient-reported changes upon BoNT treatment. To this end, we investigated the correlations between changes in mobile gait parameters and changes in clinical and patient-reported outcomes between baseline and 1-month follow-up. As the SPRS constitutes an established measure of disease severity and has been used as a primary outcome in clinical trials of HSP, we first analyzed the correlation of changes in gait analysis measures to changes in total SPRS and its subscores. There was a significant negative association of change in gait speed with change in total SPRS (Spearman $\rho = -0.3$, $p < 0.05$; Figure 2a, Table S2). The functional subscore of the SPRS (sum of items 1–6) reflects mobility-related items. There was a significant negative correlation between change in gait speed and relative swing duration to change in this subscore ($|p| > 0.3$; $p < 0.05$). Moreover, positive correlations were observed between the change in this subscore and the change in stride time and swing time, respectively. Changes in the speed of stair climbing (item 5) showed distinct positive correlations to changes in the variability of gait cycle parameters (Figure 2a, Table S2). Additionally, GAS-gait score correlated significantly with improvements in stride time (Figure 2c, Table S2). These findings align with our initial

expectations, suggesting that improvements in certain gait parameters (e.g., increased speed and reduced stride time) are associated with corresponding improvements in specific clinical aspects measured by SPRS. Contrary to our initial expectations, a negative correlation was identified between changes in variability of gait measures and changes in adductor spasticity scores as well as certain SPRS subitems (in spasticity of the adductors [item 7] and contractures of the lower limbs [item 11]; Figure 2a,b, Table S2). Regarding treatment responses of patient-reported outcome measures, there was a significant positive correlation of the SF-12 physical component score with the change of stride and stance time parameters and a significant negative correlation with the change of relative swing duration (Figure 2c, Table S2).

Machine learning assessment of treatment outcomes

We next sought to identify baseline characteristics that predicted the BoNT response, as defined by gait-related GAS score $\geq$ 2. Upon training different classifiers, the highest performance was obtained using both clinical and gait parameters at baseline (mean balanced prediction accuracy of 66% with a best result of 83%; Table S4). Notably, a similar degree of prediction was obtained when using baseline gait parameters only and omitting clinical information (mean balanced prediction accuracy of 64% with a best result of 83%). Baseline clinical parameters, on the contrary, did not sufficiently predict treatment response (balanced accuracy of 50%).

To determine the feature importance of each parameter in this model, we calculated average absolute Shapley Additive Explanations (SHAP) values. In descending order, the most important features were SPRS (SHAP=0.059; Figure 3), absolute swing time (0.039), and the variability of relative swing duration (0.037).

DISCUSSION

We studied individualized BoNT treatment effects on clinical, gait, and patient-reported parameters in HSP. We recruited a considerable cohort of HSP patients of variable degrees of disability and variable therapy goals, reflecting the “real-world” setting of specialized HSP outpatient units. Applying a standardized study protocol in three academic HSP centers on an unprecedented number of HSP patients, we demonstrated significant improvements in spasticity measures and total SPRS scores. Moreover, we characterized temporal changes of digital gait parameters and established correlations of changes in gait cycle measures to treatment response in SPRS subitems as well as physical quality of life and attainment of gait-related treatment goals. Finally, our data provide the basis for future validation studies to predict the BoNT effects in HSP.

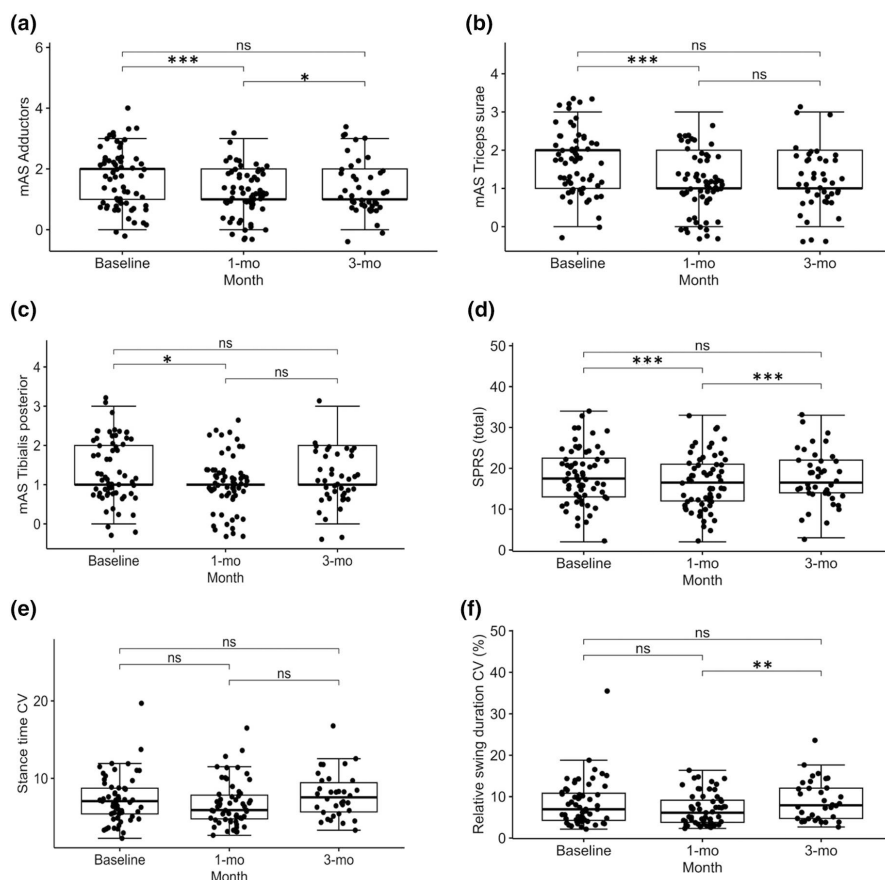


FIGURE 1 Clinical and gait variability parameters at baseline and 1 month and 3 months after botulinum neurotoxin treatment. (a) Modified Ashworth Scale (mAS) adductors. (b) mAS triceps surae. (c) mAS tibialis posterior. (d) Spastic Paraplegia Rating Scale (SPRS) total score. (e) Stance time coefficient of variation (CV). (f) Relative swing duration CV. Significant differences according to a mixed effects model are indicated by asterisks (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$). Boxes indicate median, and lower and upper quartile; whiskers indicate interquartile ranges. ns, not significant.

Clinical heterogeneity of HSP

Our cohort reflects the classical heterogeneous profile of HSP cohorts regarding age, genotype, affected muscles, and treatment goals (Table 1). Previous studies have demonstrated a wide spectrum of gait impairment in HSP regarding the spatial and temporal distribution of weakness versus spasticity and the presence of contractures and complicating symptoms like neuropathy and ataxia [27–29]. Rather than limiting our analyses to a specific subcohort or imposing a fixed treatment paradigm on the complete cohort, we applied a mixed effects model to control for confounding factors. The GAS as a patient-centered parameter of treatment response was designed to capture changes in individual goals, making it particularly useful in cases where treatment impacts may vary between patients. To this end, the GAS has been used as a primary outcome measure in BoNT studies for the management of spasticity.

BoNT effects

In the overall cohort, there was a significant reduction of spasticity in the adductors, triceps surae, and tibialis posterior at 1 month posttreatment (Table 2, Figure 1). Additionally, the HSP-specific SPRS score was significantly improved 1 month after treatment. On the other hand, no significant changes were observed in quadriceps muscle group, as it was the least frequently treated muscle group in

our cohort (Tables 1 and 2, Figure 1). One month after BoNT administration, there were nonsignificant trends toward increased walking speed, along with a trend of reduced stride time and variability of relative swing duration, particularly evident at the 1-month visit (Table 2, Figure 1). Compatible with the known temporal effects of BoNT, there were no significant changes at the 3-month time point compared to baseline. In this conservative statistical analysis, patient-reported parameters addressing functioning (SF-12) and fear of falling (FES-I) were unchanged when comparing baseline, 1-month follow-up, and 3-month follow-up, respectively (Table 2). Although these analyses were limited by missing data points, potentially leading to reduced statistical power, mean differences did not exceed previously suggested values of minimal clinically significant difference, that is, 5.1 and 5.2 for the mental and physical components of the SF-12, respectively [30–32]. Nevertheless, individual changes in the SF-12 physical component score were significantly associated with changes in gait parameters (Figure 2c, Table S2), indicating the validity of mobile digital gait analysis to reflect changes in patient-reported outcomes. Finally, we also used GAS as a gold standard anchor parameter. Our observation of significant correlations between GAS-gait scores and changes in stride time further supports the benefit of gait analysis (Figure 2c, Table S2). These observed correlations reinforce that mobile gait analysis captures treatment response in HSP.

There was an unexpected negative correlation between reduced gait variability and increased severity in specific SPRS

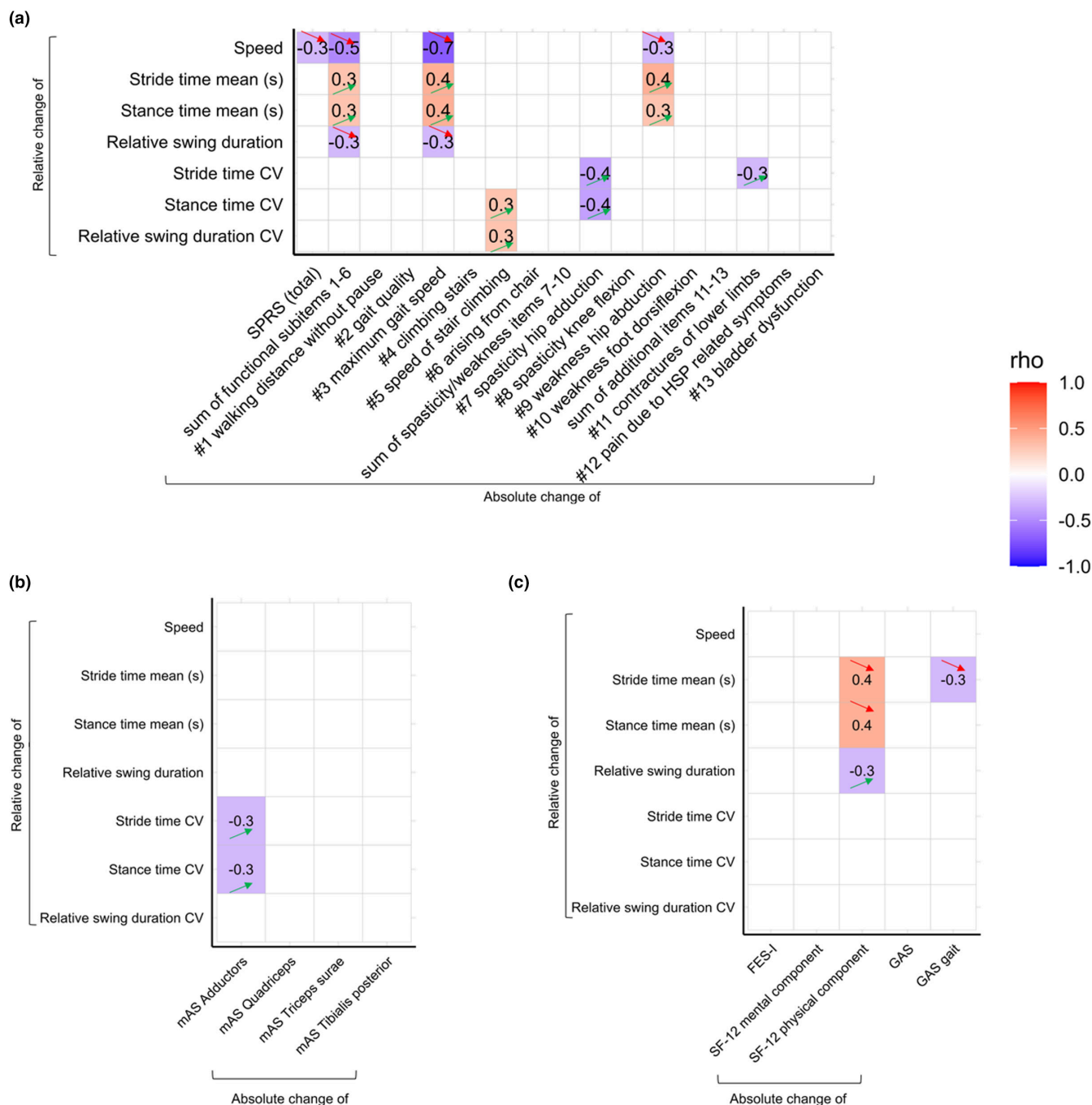


FIGURE 2 Correlation between relative changes of gait parameters and (a) absolute changes of Spastic Paraplegia Rating Scale (SPRS) subitems, (b) absolute changes of spasticity as measured by modified Ashworth Scale (mAS), (c) both values of Goal Attainment Scale (GAS) and absolute changes of patient reported Falls Efficacy Scale International (FES-I) and Short Form 12 (SF-12). Significant correlations ($p < 0.05$) only are color-coded, with ρ -values indicated inside the boxes, according to a Spearman ρ correlation. Box coloring indicates positive (red) or negative (blue) correlations, and arrows indicate whether a positive (green arrows) or a negative (red arrows) correlation would have been expected. CV, coefficient of variance; HSP, hereditary spastic paraplegia; ρ , rho correlation coefficient.

subitems. This negative correlation could be influenced by specific cases where patients exhibit improvements in objective gait parameters despite worsened clinical status. On one hand, clinical ratings may be influenced by a rater bias because ratings were performed by nonblinded neurologists. Moreover, individual patient experiences and the subjective nature of the assessment tools provide a source of bias and variability. On the other hand,

individuals with higher clinical severity may adopt more stereotyped or adaptive gait patterns as a compensatory mechanism. This could result in a reduction of gait variability despite an increase in clinical severity. This phenomenon was reported in other neurological conditions [33] and may represent a unique aspect of gait adaptation in HSP. Further investigations into the underlying mechanisms of gait adaptation in HSP are needed to elucidate

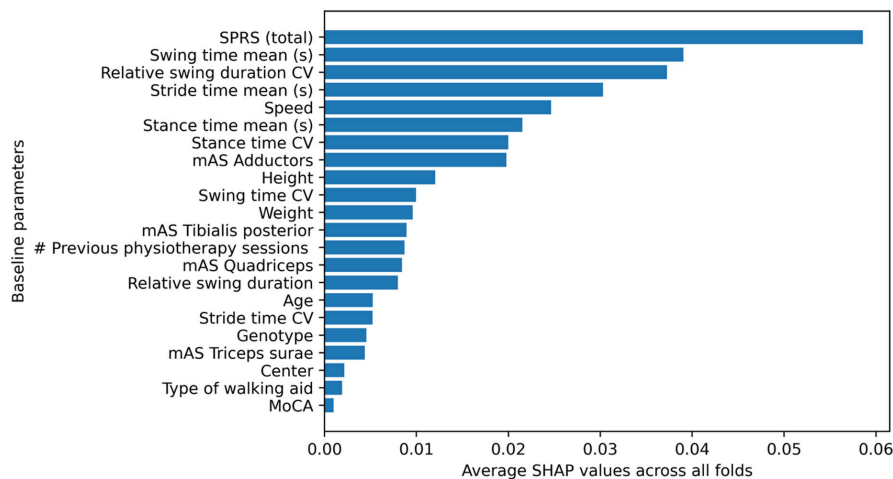


FIGURE 3 Feature contributions to the model predictions. Higher Shapley Additive Explanations (SHAP) values indicate increased importance of the corresponding baseline feature. CV, coefficient of variation; mAS, modified Ashworth Scale; MoCA, Montreal Cognitive Assessment; SPRS, Spastic Paraplegia Rating Scale.

the complex interplay between gait characteristics and clinical outcomes.

The number of previous BoNT treatment cycles was included as a covariate, and it had a significant effect on several outcome parameters, that is, treatment response was smaller in participants with first-time BoNT treatment. This difference is likely explained in that initial BoNT dosing typically starts at lower doses, and optimal dosing schemes are only established after several repeat visits. Moreover, repeat dosing is only performed in those patients who had shown beneficial effects of BoNT and no side effects. Therefore, future studies may benefit from implementing individualized dosing regimens based on patient characteristics and treatment history to maximize treatment efficacy.

Context of previous BoNT studies in HSP

The effects of BoNT in HSP have been systematically evaluated in a few studies before, as comprehensively summarized in Table S5. Servelhere et al. [34] evaluated 33 HSP patients before and 1.3 months after BoNT administration. There was no significant improvement in muscle strength, but fatigue and spasticity of the adductor muscles were improved upon BoNT treatment. Similar results were reported by Diniz de Lima et al. [28] in the to-date only placebo-controlled HSP BoNT study. The authors compared the effects of BoNT versus placebo on gait velocity, SPRS scores, spasticity, muscle strength, fatigue, pain, and patients' subjective perception of gait worsening. They identified no functional improvement of BoNT versus placebo, but the adductor muscle tone decreased significantly when compared to placebo. A limitation of this study was the fixed treatment regimen, although the study's crossover design would have permitted adaptations [29, 35]. In our study, on the contrary, we employed a patient-centered approach used in clinical routine at three centers, offering the advantage of specifically addressing each individual's spasticity-related symptoms and treatment goals.

De Niet et al. [36] evaluated the BoNT treatment of calf muscles combined with stretching exercises in 15 HSP patients. Applying a stationary motion capture system as a digital readout, they reported

improved gait velocity and reduced ankle spasticity. In a similar approach for predominant proximal leg spasticity in HSP, Van Lith et al. [37] showed that BoNT significantly improved gait speed, step width, spasticity of the hip adductor muscles, and the leg angle upon balance perturbation. In our study, 89% of patients attended at least weekly physiotherapy, and stretching as well as physical activity that was generally recommended after BoNT administration to support its biological effects [38]. Contrasting to stationary gait analysis systems, the setup used in our study was a wearable mobile system that can easily be used in different environments and at different centers.

Paparella et al. [8] studied the effect of a combined approach including both BoNT and intensive physiotherapy in 18 HSP patients. The authors reported significant improvements in spasticity, manual gait parameters, and functional measures in the majority of patients after 1 month. In line with this, we here showed similar effects in a larger multicenter cohort, applying a more conservative statistical model. Taken together, our findings are consistent with these previous studies and expand the evidence supporting the beneficial effects of BoNT in HSP.

Added benefit of digital gait parameters

Previous studies often relied on complex gait analysis methods like motion capture systems and electronic gait mats. In contrast, we used validated wearables [9, 17], streamlining data collection and making it more accessible. This approach is particularly useful for multicenter trials and could be extended to home environments for understanding individual treatment responses to BoNT therapy, and to gain more insight regarding at which point reinjection visits are required. However, real-world complexity, including environmental factors, will necessitate customized algorithms and cautious data interpretation.

Our multicenter design paves the way for future randomized controlled trials in HSP treatment. The application of machine learning for predicting treatment response represents a novel approach in HSP treatment studies that may identify patterns and predictive

factors that might remain unnoticed in traditional clinical assessments, enhancing our understanding of treatment response variability and leading to more effective outcomes.

CONCLUSIONS

In conclusion, our study provides preliminary evidence for the beneficial effects of BoNT on clinical and gait parameters in ambulatory HSP patients. Our findings underscore the potential of mobile digital gait analysis as a valuable tool in monitoring and quantifying treatment outcomes, thereby paving the way for more personalized and effective therapeutic strategies in HSP management.

AUTHOR CONTRIBUTIONS

Alzhraa A. Ibrahim: Data analysis; writing of first manuscript draft; review of manuscript. **Malte Ollenschläger:** Data analysis; review of manuscript. **Stephan Klebe:** Study conceptualization; recruitment and treatment of patients; review of manuscript. **Rebecca Schüle:** Study conceptualization; recruitment and treatment of patients; review of manuscript. **Nicole Jeschonneck:** Recruitment and coordination of patients; review of manuscript. **Melanie Kellner:** Recruitment and treatment of patients; review of manuscript. **Evelyn Loris:** Data collection; review of manuscript. **Teresa Greinwalder:** Data collection; review of manuscript. **Bjoern M. Eskofier:** Conceptualization and implementation of machine learning algorithm; review of manuscript. **Jürgen Winkler:** Study conceptualization; recruitment and treatment of patients; review of manuscript. **Heiko Gaßner:** Study conceptualization; review of manuscript; supervision of gait analyses and data analysis. **Martin Regensburger:** Study conceptualization; recruitment and treatment of patients; data collection; supervision of data analysis; writing of first manuscript draft; review of manuscript.

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CONFLICT OF INTEREST STATEMENT

M.O. is employed by Portables HealthCare Technologies, which develops and markets the mobile GaitLab system. B.M.E. is co-owner of Portables HealthCare Technologies, Portables, and Procurement and holds patent EP 16174268.9 on gait assessment. All other authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

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