Gait & Posture 114 (2024) 270–276

Contents lists available at ScienceDirect

Gait & Posture

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

Are clinical tests and biomechanical measures of gait stability able to differentiate fallers from non-fallers in hereditary spastic paraplegia?

Lotte van de Venis [a,b,*], Jean Ormiston [c], Sjoerd Bruijn [d], Alexander C.H. Geurts [a,b], Bart P.C. van de Warrenburg [e], Vivian Weerdesteyn [a,c], Noël Keijsers [c], Jorik Nonnekes [a,b]

[a] Radboud University Medical Center; Donders Institute for Brain, Cognition and Behavior; Department of Rehabilitation; Nijmegen, the Netherlands
[b] Department of Rehabilitation, Sint Maartenskliniek, Nijmegen, The Netherlands
[c] Department of Research, Sint Maartenskliniek, Nijmegen, The Netherlands
[d] Department of Human Movement Sciences, Faculty of Behavioural and Movement Sciences, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands
[e] Radboud University Medical Center; Donders Institute for Brain, Cognition and Behavior; Department of Neurology; Nijmegen, the Netherlands

ARTICLE INFO

Keywords:
Hereditary spastic paraplegia
Balance
Gait
Rehabilitation

ABSTRACT

Introduction: Balance and gait impairments are common in people with hereditary spastic paraplegia (HSP) and often result in falls. Measures that identify patients at risk of falling are clinically relevant, but relatively unexplored in HSP. Here, we evaluated the potential of different balance and gait constructs to (1) identify differences between healthy controls and people with HSP and (2) discriminate between fallers and non-fallers with HSP.

Methods: We included 33 people with pure-HSP and 15 healthy controls. We assessed balance confidence (six-item Activities-specific Balance Confidence scale), clinical balance capacity (Mini-Balance Evaluation Systems Test) and gait capacity (ten-meter Walk Test). Biomechanical measures included spatiotemporal gait variability, mediolateral Margin of Stability (MoS), Foot Placement Deviation (FPD), and Local Divergence Exponents (LDEs) of trunk and pelvis, derived from treadmill-walking at comfortable and fixed gait speeds. People with HSP logged their falls during a fifteen-week period and were categorized as 'faller' (≥1 fall) or 'non-faller'.

Results: People with HSP had significantly lower balance confidence, balance capacity, and gait capacity compared to age-matched controls. People with HSP also showed reduced gait stability, reflected by increased spatiotemporal gait variability, FPD, and LDEs of trunk and pelvis. Overall, 44 % of people with HSP were categorized as 'faller'. Balance confidence (AUC:0.84) and balance capacity (AUC:0.75) discriminated fallers from non-fallers, whereas none of the biomechanical measures significantly differed.

Conclusion: Balance confidence, clinical balance and gait capacity, and biomechanical measures are affected in HSP, but clinical measures showed potential to differentiate fallers from non-fallers in people with HSP.

1. Introduction

Hereditary spastic paraplegia (HSP) comprises a heterogenous group of neurodegenerative disorders. Pure forms of HSP are clinically characterized by progressive bilateral spasticity, muscle weakness, and loss of proprioception of the lower extremities [1]. Due to these symptoms, balance and gait impairments are common, disabling and often result in fear-of-falling, falls, and fall-related injuries [2,3]. In order to optimally tailor fall prevention interventions, the clinical field is in need of accurate and useful measures that can identify individuals with HSP who exhibit a propensity for falling, and those who do not.

Fall risk can be assessed using different constructs: balance confidence is used to assess perception of fall risk through patient-reported outcomes (e.g., the Activities-specific Balance Confidence scale (ABC)) [4,5], whereas objective clinical measures are used to assess general balance capacity (e.g., Mini Balance Evaluations Systems Test (Mini-BEST)) [4,6] or gait capacity (e.g., self-selected gait speed during the ten-meter walk test) [7]. Moreover, biomechanical measures of gait stability (e.g., spatiotemporal gait variability, mediolateral Margin of Stability (MoS), mediolateral Foot Placements Deviation (FPD), and Local Divergence Exponents (LDEs)) can objectify detailed aspects of dynamic balance capacity [8].

* Correspondence to: Radboud University Medical Center, PO Box 9101, Nijmegen 6500 HB, the Netherlands.
E-mail address: lotte.vandevenis@radboudumc.nl (L. van de Venis).

https://doi.org/10.1016/j.gaitpost.2024.10.017
Received 6 December 2023; Received in revised form 24 July 2024; Accepted 15 October 2024
Available online 16 October 2024

The potential of the aforementioned measures has been evaluated in various neurological populations, although most of these studies evaluated their ability to discriminate patients from healthy controls. A few studies have been performed to differentiate fallers from non-fallers; the construct of self-perceived balance confidence showed acceptable differentiating potential in people with Parkinson's Disease [9,10], dystonia [11] and stroke [12], whereas the construct of general balance capacity showed acceptable to excellent differentiating potential in people with Parkinson's Disease [9,10]. Similar results have been reported for biomechanical measures of gait stability. Compared to non-fallers, fallers exhibited higher spatiotemporal gait variability in a cohort with cerebellar ataxia [13]. Fallers additionally showed higher LDEs in cerebellar ataxia [14], a mixed cohort in neurological patients with paresis of the lower extremities [15], and multiple sclerosis [16,17]. Lastly, fallers exhibited decreased mediolateral MoS in multiple sclerosis [16]. The FPD has not yet been evaluated as a measure to differentiate fallers from non-fallers, but was increased in people with incomplete spinal cord injury compared to healthy controls[18].

Even though the aforementioned studies offer important insights into potential measures that could indicate when persons with neurological conditions exhibit a propensity for falling, their potential to discriminate between fallers and non-fallers in people with HSP has not been evaluated. To fill this gap, the current study evaluates the potential of both the clinical and biomechanical balance and gait measures for the fall risk assessment in ambulatory people with pure HSP. To this end, we assessed the different constructs, i.e., subjective balance confidence, objective clinical balance and gait capacity, and biomechanical measures of gait stability. As a first explorative step, we evaluated whether these constructs differed between people with pure HSP and healthy age-matched controls. Second, we divided the HSP cohort into fallers and non-fallers based on their real-life fall incidence and assessed the ability of these constructs to discriminate between fallers and non-fallers among people with HSP.

2. Methods Participants and setting

This study was part of the data collection in a randomized clinical trial [19,20]. Specifically, we obtained fall rates logged by the participants in the fifteen weeks prior to the first assessment. Participants were recruited via the Center of Expertise for Rare and Genetic Movement Disorders of the Radboudumc - part of the European Reference Network for Rare Neurological Diseases (ERN-RND) - and via the HSP patient organization "Spierziekten Nederland". Participants with HSP were found eligible if they met the following inclusion criteria: (i) diagnosis of pure HSP made by a movement disorders neurologist, based on inheritance pattern, clinical examination, and when available, the molecular diagnosis. Pure HSP is here defined as persons with HSP that present with bilateral spasticity, muscle weakness, and loss of proprioception of the lower extremities. In contrast, complex HSP is defined as persons with HSP that present with additional neurological symptoms – such as ataxia, optic atrophy, or mental retardation, (ii) aged between 18 and 70 years old, and (iii) being able to walk barefoot on a level ground for 50 m without a walking aid during the assessment (use of orthopedic shoes and orthotic devices was allowed). Exclusion criteria consisted of (i) any concomitant neurological, orthopedic or psychiatric condition affecting balance or gait performance and (ii), any HSP-related surgical procedure of the lower extremities in the medical history. For the current study, 33 of the 36 participants with pure HSP (age: 48.7±11.3 years, 73 % male) were included: three participants were excluded as they were unable to walk on the treadmill. Additionally, fifteen healthy control participants (i.e., without neurological of orthopedic impairments) of comparable age and sex (age: 49.0 ±11.5 years, 73 % male) were recruited from the community. The study was approved by the ethical committee Oost-Nederland and all participants provided written informed consent. Participants visited the movement laboratory of the Radboudumc (Nijmegen, The Netherlands) once.

2.1. Fall assessment

Prior to the assessment, participants with HSP logged their falls for fifteen weeks. We used a prospective recording method, where participants had on demand access to a digital fall diary. Participants were instructed and encouraged to report the occurrence of a fall as soon as possible. Every other week, participants were contacted via a phone call by the primary investigator (LvdV) to remind them to fill out the fall diary, and confirm the falls that had been entered previously. During the fifteen weeks, participants were allowed to use their walking aids and orthotics as usual. For this study, a fall was defined as an event that resulted in a person coming to rest inadvertently on a lower level surface [21]. Falls that occurred while playing sports were excluded. Based on these data, participants with HSP were either classified as 'fallers' (if they had logged one or more falls) or as 'non-fallers' (if they had not logged any falls).

2.2. Clinical assessment

Balance confidence was assessed with the six-item version of the Activities-specific Balance Confidence scale (ABC-6) [22]. Balance capacity was evaluated with the Mini Balance Evaluation Systems Test (Mini-BEST) [23], and gait capacity with the 10-meter Walk Test (10mWT) performed at both comfortable gait speed and at maximum gait speed [24]. As a clinical descriptor, disease severity in people with HSP was assessed with the Spastic Paraplegia Rating Scale (SPRS), where higher scores indicate greater disease severity (range 0–52) [25]. Furthermore, to gain insight in the amount of time that people with HSP spent walking on a daily basis, an activity monitor was placed on their right upper leg (Activ8, Remedy Distribution Ltd., Valkenswaard, the Netherlands) for seven consecutive days following the assessment.

2.3. Biomechanical assessment

In order to obtain the biomechanical measures of gait stability, a gait analysis was performed on an instrumented treadmill (M-gait dual-belt treadmill with two embedded force plates, Motek Medical, The Netherlands). We extracted the following biomechanical measures: i) variability of step length, step time and step width [8], ii) medio-lateral margin of stability (MoS) [26], iii) adherence to the medio-lateral foot placement strategy through foot placement deviations (FPD) [18], and iv) local dynamic stability through maximum local divergence exponents (LDEs)[27]. All measures are further explained below. In line with the standard upper and lower body plug-in-gait model, 39 reflective markers were placed on anatomical landmarks. Thereafter, the individual comfortable treadmill speed was determined: the treadmill speed was gradually increased until the participant stated that it felt comfortable. Then, treadmill speed was increased by 0.3 ms^{-1} before gradually decreasing the speed until participants again stated they walked at their comfortable speed [17,28]. The average speed of both assessments was selected as the individual comfortable gait speed. All participant (i.e., persons with HSP, and the healthy controls) performed two three-minute walking trials at comfortable gait speed. Participants with HSP performed two additional trials of three-minute treadmill walking at a fixed speed of either 0.6 ms^{-1} or 0.8 ms^{-1}. In contrast, healthy controls performed four additional trials of three-minute treadmill walking trials: two trials at the fixed speeds of 0.6 ms^{-1}, and two trials at the fixed speed of 0.8 ms^{-1}. All participants were instructed to walk as comfortable as possible without holding onto the treadmill bars. Participants with HSP wore their own (orthopedic) shoes and orthotics if required. Kinematic data were collected using a 10-camera 3-dimensional motion capture system (Vicon Nexus, Oxford, UK) at a sampling rate of 100 Hz. The treadmill was equipped with two force plates sampling at a rate of 2000 Hz. Details of the kinematic data processing can be found in Supplementary Explanations A.1.

Prior to calculating the biomechanical measures, walking trials were

checked for events where participants lost balance and needed to hold onto the bars. The steps occurring during these events were removed, in addition to two additional steps prior to and following the event. This was done to ensure that the biomechanical measures reflected the participants' ability to independently recover from small perturbations, without these measures being influenced by the external support that the bars provided. Heel strikes were identified as the moment of heel marker position minima in the vertical direction during a gait cycle. Step length and step time were calculated between two subsequent heel strikes (i.e., from left heel strike to right heel strike, and vice-versa). Step width was calculated as the distance between the left and right heel markers at 50 % of mid stance. The mean and standard deviation of the spatiotemporal measures were calculated over the valid left and right steps collected during two similar three-minute walking trials.

2.3.1. Spatiotemporal gait variability

Gait variability was expressed in the coefficient of variation (CoV) for step length, step time and step width using the following equation:

$$Coefficient\ of\ Variation = \frac{Standard\ deviation}{Mean} * 100\% \quad (1)$$

2.3.2. Medio-lateral margin of stability

MoS was calculated in the mediolateral direction using the following equation[29], and defined as its minimum value during single stance:

$$MoS = BoS - XCoM \quad (2)$$

The base of support (BoS) was defined as the position of the mediolateral center of pressure (CoP) using the force plate recordings [26]. The extrapolated center of mass (XCOM) was calculated according to Hof et al[29]. for which the position of the center of mass (CoM) was extracted from VICON. The mean MoS was calculated over the valid left and right steps collected during the three-minute walking trials, whereas variability of MoS was calculated using standard deviation.

2.3.3. Foot placement deviation

A previous study showed that the optimal mediolateral foot placement of the next step can be predicted based on the mediolateral CoM position and CoM velocity at mid stance[30]. To evaluate whether people with HSP can adhere to this optimal foot placement strategy, we calculated foot placement deviations using the root mean square error (RMSE) between the predicted and actual foot placements[18]. To this end, we calculated the predicted foot placement in mediolateral direction based on the medio-lateral CoM position and velocity at heel strike using the following equation[18]:

$$Predicted\ foot\ placement = \beta_{position} * CoM + \beta_{velocity} * CoM' + \varepsilon \quad (3)$$

where the $\beta_{position}$ and $\beta_{velocity}$ are defined as the regression coefficients, and ε as the model error.

The actual foot placement was calculated as the centered mediolateral distance (i.e., subtracting the general mean from each individual step) between the left and right heel markers at midstance[18].

2.3.4. Local dynamic stability

To assess local dynamic stability, the revised Rosenstein algorithm was used to calculate maximum local divergence exponents (LDEs)[8,27]. LDEs were calculated for the trunk and pelvis over one step (i.e., the so-called short-LDE) in the anterior-posterior, medio-lateral and vertical directions. For this purpose, the trunk was defined as the midpoint between the processus spinosus of the 7th cervical vertebra (i.e., C7-marker) and the manubrium sterni (i.e., CLAV-marker). The pelvis was defined as the midpoint between the center of the left and right spina iliaca posterior superior and the left and right spina iliaca anterior superior (i.e., LPSI, RPSI, LASI and RASI-markers, respectively). For each participant, the LDEs of the raw velocity of the spatially filtered trunk and pelvis trajectories were calculated over 65 strides per trial, as this was the maximum available number of strides across all participants. Further details on the calculation of the LDEs can be found in supplementary explanation A.2.

2.4. Statistical analysis

All analyses were conducted using IBM SPSS statistics (version 25) software. Data were first checked for normality using Shapiro-Wilk Test. Then, a series of independent samples t-tests (or Mann-Whitney U tests when appropriate) were used to assess differences between participants with HSP and healthy controls. To correct for multiple testing, level of significance was set at $p < 0.01$. Group differences were assessed for subjective balance confidence, objective clinical balance and gait capacity tests, and the biomechanical measures of gait stability derived from walking trials at comfortable gait speed.

As most biomechanical measures of gait stability are known to be speed-dependent[7,31,32], we repeated the analyses for both groups when walking at the same fixed treadmill speed. In these analyses, we only included participants with HSP who were able to perform the additional fixed-speed trials at either 0.6 ms^{-1} or 0.8 ms^{-1}. We assessed the distribution of 0.6 ms^{-1} and 0.8 ms^{-1} among these participants with HSP, and pseudo-randomly selected a similar distribution of the 0.6 ms^{-1} and 0.8 ms^{-1} trials from the healthy controls.

Lastly, differences between fallers and non-fallers among participants with HSP were assessed. First, a series of independent samples t-tests (or Mann-Whitney U tests when appropriate) were used to assess differences between fallers and non-fallers regarding the clinical capacity and gait stability measures extracted from the walking trials at comfortable gait speed. The ability of these measures to discriminate fallers from non-fallers was evaluated using the area under the curve (AUC) of the receiving operating characteristics curve (ROC). An AUC $\geq$0.9 was considered outstanding discrimination, $\geq$0.8 to <0.9 excellent discrimination, $\geq$0.7 to <0.8 acceptable discrimination, and <0.7 poor discrimination[33].

3. Results

3.1. Participants

A molecular diagnosis was available for 26 of the 33 participants with HSP (SPG4 (n=23); SPG5A (n=1); SPG8 (n=1); NEFL (n=1)). The mean SPRS score of the whole group was 10.1±3.9 points. The mean time since first symptom onset was 16±13 years. A total of three participants with HSP used orthopedic shoes, whereas four participants with HSP used posterior ankle-foot orthotics (bilaterally) to perform the walking trials on the treadmill. Participants with HSP and healthy controls did not differ in age or sex.

3.2. Clinical assessment

Participants with HSP scored significantly worse on the ABC-6, Mini-BEST, and 10mWT compared to healthy controls (Table 1).

3.3. Biomechanical assessment at comfortable walking speed

Participants with HSP showed a slower comfortable treadmill speed than the healthy controls (0.88 ± 0.26 ms^{-1} vs. 1.31 ± 0.11 ms^{-1}; $p<0.001$). Five participants with HSP used the treadmill bars occasionally to restore balance (one participant one time, one participants two times, two participants five times, and one participant eight times). None of the healthy controls used the treadmill bars. People with HSP also showed significantly greater variation of step length and step time (Table 1). In line with these results, the foot placement deviation and the LDE of the trunk in mediolateral direction, and the LDEs of the pelvis in anteroposterior and vertical direction were significantly higher in participants with HSP compared to healthy controls (Table 1). The MoS

Table 1
Differences between participants with HSP and healthy controls regarding clinical and biomechanical measures at comfortable treadmill velocity.

	HSP (n=33)	HC (n=15)	P-value
Clinical assessment			
Activities-specific Balance Confidence scale – six-item	56 ± 23	92 ± 78	< 0.001
Mini-BEST	19.5 ± 4.5	27.0 ± 1.0	< 0.001
Ten-meter walk test – comfortable (ms^{-1})	1.3 ± 0.3	1.6 ± 0.2	< 0.001
Ten-meter walk test – fast (ms^{-1})	1.7 ± 0.3	2.4 ± 0.4	< 0.001
Biomechanical assessment			
Step width (mm)	125 ± 44	94 ± 33	0.021
Coefficient of variation			
· Step length (%)	7.3 ± 5	2.4 ± 0.6	< 0.001
· Step time (%)	4.9 ± 3	2.1 ± 0.5	< 0.001
· Step width (%)	27.5 ± 13	27.1 ± 13.4	0.973
Mediolateral Margin of Stability (MoS) (mm)	45.8 ± 17	47.6 ± 10.6	0.696
Variability of MoS (mm)	13.4 ± 8	14.3 ± 6.8	0.368
Mediolateral Foot Placement Deviation (cm)	1.0 ± 0.3	0.7 ± 0.2	< 0.001
Local Divergence Exponents			
· Trunk - mediolateral	1.5 ± 0.3	1.8 ± 0.2	< 0.001
· Trunk - anteroposterior	1.7 ± 0.3	1.6 ± 0.2	0.019
· Trunk - vertical	1.4 ± 0.2	1.3 ± 0.1	0.013
· Pelvis - mediolateral	1.3 ± 0.2	1.1 ± 0.2	0.064
· Pelvis - anteroposterior	1.5 ± 0.3	1.3 ± 0.2	0.008
· Pelvis - vertical	1.3 ± 0.2	1.2 ± 0.1	0.008

Values displayed are means ± standard deviation. Abbreviations: Mini-BEST: Mini Balance Evaluation Systems Test. Mini-BEST ranges between 0 and 28 points; Activities-specific Balance Confidence scale – six-item ranges between 0 and 100 points.

outcomes did not differ between groups.

3.4. Biomechanical assessment at fixed walking speed

A total of 24 participants with HSP were able to perform the additional trials at a slower fixed speed of either 0.6 ms^{-1} (n=16) or 0.8 ms^{-1} (n=8). Nine participants were unable to perform these additional trials: five participants were too fatigued, and four participants already had a self-selected walking speed below 0.6 ms^{-1}. To provide insight in whether this imposed a selection bias of this subgroup (i.e., only the best 'walkers' remained in the analysis), we included the scores of balance confidence, balance capacity and gait capacity test of the selected participants in supplementary Table A.1. This shows that the subgroup of 24 participants performed more or less the same on the clinical tests compared to the full cohort of 33 participants (ABC: 59±23 vs. 56±23 points; MiniBEST: 20±4 vs. 20±5 points; 10mWT at comfortable gait speed: 1.3±0.3 vs. 1.3±0.2 ms^{-1}, respectively). Of the 24 participants included in this analysis, five patients with HSP used the treadmill bars to restore balance (four participants one time, one participant two times). None of the healthy controls used the treadmill bars. To perform the statistical analysis, we individually matched the slow fixed speed trials performed by the HSP participants with trials from the healthy control group: ten at the fixed speed of 0.6 ms^{-1} and five at the fixed speed of 0.8 ms^{-1}. The coefficient of variation of step length and step time remained significantly higher among participants with HSP compared to healthy controls. In addition, participants with HSP showed significantly greater LDE of the trunk in vertical direction and MoS variability (supplementary Table A.1).

3.5. Differences between fallers and non-fallers

A total of 32 participants with HSP returned a completed fall-diary over a period of fifteen weeks; one participant experienced technical difficulties. Of these 32 participants, 14 (44 %) reported one or more falls and were categorized as 'fallers'. The reported fall rates ranged between 1 and 5 falls per participant (1 fall (n=7); 2 falls (n=2); 3 falls (n=1); 4 falls (n=3) and 5 falls (n=1)). The remaining 18 participants did not report any falls and were categorized as 'non-fallers'. Fallers and non-fallers did not differ in terms of age (50 ± 9 vs. 48 ± 13; p=0.70), sex (71 % vs 78 % males; p=0.68), time since first symptom onset (19 ±12 years vs. 12±10 years, p=0.084), SPRS scores (11.2 ± 4.1 vs. 9.1 ± 3.6, p=0.145), or the percentage spent walking on a daily basis (7.4 % ± 2.8 vs. 9.0 % ± 3.1, p=0.15). Two fallers (14 % of fallers) used the treadmill bars to restore balance (one participant two times, one participant eight times), whereas three non-fallers (17 % of non-fallers) used the treadmill bars (one participant one time, two participants five times). Moreover, the comfortable treadmill speed did not significantly differ between fallers and non-fallers (0.84 ± 0.31 ms^{-1} vs. 0.92 ± 0.22 ms^{-1}; p=0.39). Fallers scored significantly worse on the ABC-6 compared to non-fallers (p=0.001), and the ABC showed excellent discrimination between fallers and non-fallers (AUC = 0.84). Furthermore, the Mini-BEST showed acceptable discriminatory ability between fallers and non-fallers fallers scored significantly worse on the Mini-BEST compared to non-fallers (AUC = 0.75). The gait capacity and gait stability measures showed poor discriminatory ability between fallers and non-fallers (AUCs < 0.70; Table 2).

4. Discussion

This exploratory cohort study provides insight in the potential of various constructs - i.e., subjective balance confidence, objective clinical balance and gait capacity tests, and several promising biomechanical measures of gait stability - to discriminate between fallers and non-fallers among people with HSP. As a first step, we compared outcomes between people with HSP and healthy age-matched controls. We found that subjective balance confidence (ABC-6), objective clinical balance and gait capacity (Mini-BEST and 10mWT), and multiple biomechanical measures (spatiotemporal variability of step length and step time, FPD, and LDEs of the trunk) were significantly poorer in people with HSP compared to healthy controls. Subsequently, we compared the outcomes between fallers and non-fallers in HSP. Subjective balance confidence (ABC-6) showed excellent discriminative ability and objective clinical balance capacity (Mini-BEST) showed acceptable discriminative ability, whereas none of the biomechanical measures of gait stability were able to differentiate between fallers and non-fallers in HSP.

It is not surprising that people with HSP showed decreased balance confidence (ABC-6), balance capacity (Mini-BEST), and gait capacity (10mWT) compared to healthy controls, as these findings are in line with the literature[2,3,34–36]. The observed greater variability of spatiotemporal gait parameters in people with HSP compared to

Table 2
Differences between fallers and non-fallers regarding clinical and biomechanical measures at comfortable treadmill velocity.

	Fallers(n=14)	Non-Fallers (n=18)	P-value	AUC
Clinical Assessment				
Activities-specific Balance Confidence scale – six-item	44 ± 19	78 ± 14	0.001	0.837
Mini-BEST	17.6 ± 4.1	20.8 ± 4.5	0.046	0.750
Ten-meter walk test – comfortable (ms^{-1})	1.2 ± 0.3	1.4 ± 0.2	0.081	0.659
Ten-meter walk test – fast (ms^{-1})	1.6 ± 0.4	1.8 ± 0.3	0.251	0.615
Biomechanical assessment				
Step width (mm)	135 ± 43	120 ± 44	0.350	0.433
Coefficient of variation				
Step length (%)	7.4 ± 5.7	7.2 ± 5.3	0.808	0.472
Step time (%)	5.7 ± 0.4	4.5 ± 2.1	0.587	0.560
Step width (%)	27.3 ± 14.9	26.8 ± 12.5	0.925	0.488
Mediolateral Margin of Stability (MoS) (mm)	40.3 ± 17.7	51.2 ± 15.2	0.071	0.690
Variability of MoS (mm)	13.3 ± 8.8	13.7 ± 7.7	0.866	0.480
Mediolateral Foot Placement Deviation (cm)	1.0 ± 0.3	1.0 ± 0.3	0.377	0.595
Local Divergence Exponents				
Trunk - mediolateral	1.8 ± 0.4	1.8 ± 0.3	0.878	0.480
Trunk - anteroposterior	1.7 ± 0.2	1.8 ± 0.3	0.737	0.500
Trunk - vertical	1.4 ± 0.2	1.4 ± 0.2	0.764	0.464
Pelvis - mediolateral	1.3 ± 0.2	1.3 ± 0.2	0.706	0.563
Pelvis - anteroposterior	1.5 ± 0.2	1.4 ± 0.3	0.574	0.560
Pelvis - vertical	1.3 ± 0.2	1.3 ± 0.1	0.266	0.611

Values displayed are means ± standard deviation. Abbreviations: Mini-BEST: Mini Balance Evaluation Systems Test. Mini-BEST ranges between 0-28 points; Activities-specific Balance Confidence scale – six-item ranges between 0-100 points.

age-matched controls is also in line with the literature[37]. Although no studies have assessed FPD or LDEs in people with HSP, previous studies did report a higher FPD in people with incomplete spinal cord injury [18], and higher LDEs in a mixed neurological cohort[15] compared to healthy controls. In contrast, a previous study found reduced medio-lateral MoS at midstance in HSP[38], whereas we did not find such differences between both groups. These contrasting results might be due to differences in disease severity of the included participants, but unfortunately this assumption cannot be verified as no measure of disease severity was reported in the study by van Vugt et al[38].

It may be argued that differences in biomechanical measures between HSP and controls emerged as a result of differences in gait speed. Indeed, comfortable gait speed was significantly lower in people with HSP, and earlier studies have demonstrated that gait speed affects gait stability[31,32,39,40]. To make a speed-controlled comparison between HSP and controls, we asked both groups to walk at a similar, fixed gait speed. For these conditions, we still found that people with HSP walked with greater variability of step length and step time. Furthermore, we found greater variability of the mediolateral MoS, and a larger LDE of the trunk in vertical direction) in HSP compared to controls. These findings indicate that the observed differences in stability measures at comfortable gait speed cannot merely be explained by speed differences, but (at least partly) reflect true differences in gait stability.

Interestingly, our data show that balance confidence (as measured with the ABC-6), had the best potential to discriminate between fallers and non-fallers with HSP. Previous studies also reported that ABC or ABC-6 is able to differentiate fallers from non-fallers in people with multiple sclerosis (AUC: 0.92)[5], Parkinson's disease (AUC: 0.73)[10], stroke (AUC: 0.78)[12], and dystonia (AUC: 0.72)[11]. Our data additionally show that balance capacity as assessed with the Mini-BEST may be a good objective clinical test for fall risk assessment in people with HSP. It's ability to discriminate fallers from non-fallers has previously been reported in people with Parkinson's disease (AUC: 0.75–0.86) [6,9,41], myotonic dystrophy (AUC: 0.83)[42], and in the elderly (AUC: 0.72–0.80)[43,44]. Therefore, for the purpose of fall screening among people with HSP, the current results indicate the potential value of subjective balance confidence (ABC-6) and objective balance capacity (MiniBEST) as useful tools. This may provide preliminary guidance for clinicians to monitor and identify fallers from non-fallers among people with HSP in daily clinical practice.

In contrast to the discriminatory ability of the ABC-6 and the Mini-BEST, we did not find similar evidence for any of the gait capacity or biomechanical measures. This is in contrast to recent studies that reported increased LDEs when comparing fallers and non-fallers in the elderly[45,46] and in people with multiple sclerosis[16,17]. The question remains why the biomechanical measures were unable to discriminate between fallers and non-fallers in HSP. In order not to fall, people have to be able to recover from both small perturbations that occur during every step (e.g. resulting from heel strike), and larger perturbations (e.g. when tripping over an obstacle)[8]. In the current study, the biomechanical measures were derived from unperturbed treadmill walking. Therefore, the biomechanical measures primarily reflect the ability to recover from small perturbations[8]. In contrast, the Mini-BEST includes tasks that impose greater challenges than unperturbed walking, and includes both proactive and reactive balance control. These perturbations are more representative of those encountered in daily life, and as such, more representative of those resulting in falls. This difference may partly explain the higher discriminatory ability of the Mini-BEST compared to the treadmill-based biomechanical measures of gait stability in this study. Therefore, future studies could explore whether biomechanical measures have the ability to capture individual deficits contributing to falls when derived from daily life walking.

Apart from the biomechanical considerations above, our study has some methodological limitations. Participants with HSP logged their falls using a fall diary prior to the assessment[20]. As a result, fallers answered the questions of the ABC-6 after they had experienced a fall, which may have affected their confidence. Future research could evaluate the predictive validity of ABC-6 for fall risk assessment in people who have not yet experienced a fall. Furthermore, previous studies have shown that a fall in the preceding year is a strong predictor for future falls[47,48]. Unfortunately, we were unable to collect fall data of the year preceding our assessment, as this timespan partly coincided with the fifteen-week fall diary. Moreover, we were unable to maintain a fall diary following the assessment in order to examine predictive efficacy of the assessed measures. We did not ask about perceived risk of falling to assess whether fallers were conscious of their own susceptibility of falling. Lastly, we did not include a validation cohort to confirm our findings.

5. Conclusion

In conclusion, our results show that in HSP, the ABC-6 and Mini-BEST are useful clinical measures to differentiate potential fallers from non-fallers. These findings may provide a preliminary guideline for fall screening in HSP in daily clinical practice. Our findings also provide insight in the potential usefulness of the applied outcome measures for trials investigating the effectiveness of fall-prevention interventions. As a next step, future studies could evaluate the potential of biomechanical measures in a free-living environment that encompasses the challenging circumstances during which falling usually occurs. Recently, it has been reported that stride characteristics in people with HSP can effectively be evaluated by using wearable inertial gait sensors in a controlled clinical environment and that the so-obtained data are associated with disease severity and progression[37]. Yet, it remains to be investigated whether real-life gait assessment using inertial gait sensors is able to improve fall risk assessment and select targeted interventions.

Ethical Compliance Statement

The study was conducted in line with the requirements of the medical ethical committee review – Regio Oost-Nederland, Nijmegen, The Netherlands. All participants provided written informed consent prior to any study procedure. 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.

Financial disclosures

L.V., J.O., and A.G. declare there are no disclosures to report. J.N. reports grants from ZonMW (OffRoad grant, Veni Grant, TopZorg Grant), Ipsen Pharmaceuticals, and Parkinson Foundation. outside the submitted work. S.M.B. was funded by a VIDI grant from the Dutch Organization for Scientific Research (NWO). V.W. holds research funding from The Netherlands Organisation for Scientific Research (NWO; Vidi grant); The Netherlands Organisation for Health Research and Development (ZonMW; TZO and IMDI grant); and Interreg NWE. B.W. has received research funds from Radboud University Medical Center, ZonMw, Dutch Research council (NWO), Hersenstichting, and the Gossweiler Foundation. N.K. reports grant from ZonMW (Topzorg), NOW-TTW (Exo-aid), Interreg (VR4Rehab, Motion), EFRO (GUTS), AAL (NEST), LSHM (GaReC, MOTOR).

Funding

The work was supported by the Jacques und Gloria Gossweiler Foundation. The funders were not involved in the development of the protocol, nor were they involved in the execution, analyses or interpretation of the study data.

CRediT authorship contribution statement

Alexander C.H. Geurts: Writing – review & editing, Methodology, Conceptualization. **Bart P.C. van de Warrenburg:** Writing – review & editing, Methodology, Conceptualization. **Jean Ormiston:** Writing – review & editing, Methodology, Formal analysis. **Sjoerd Bruijn:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Jorik Nonnekes:** Writing – original draft, Visualization, Supervision, Methodology, Conceptualization. **Lotte van de Venis:** Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft. **Vivian Weerdesteyn:** Writing – review & editing, Methodology, Conceptualization. **Noël Keijsers:** Writing – review & editing, Methodology, Formal analysis, Conceptualization.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest relevant to this work.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.gaitpost.2024.10.017.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

[1] S. Shribman, et al., Hereditary spastic paraplegia: from diagnosis to emerging therapeutic approaches, Lancet Neurol. 18 (12) (2019) 1136–1146.
[2] B.J.H. van Lith, et al., Experienced complaints, activity limitations and loss of motor capacities in patients with pure hereditary spastic paraplegia: a web-based survey in the Netherlands, Orphanet J. Rare Dis. 15 (1) (2020) 64.
[3] J. Nonnekes, et al., Pathophysiology, diagnostic work-up and management of balance impairments and falls in patients with hereditary spastic paraplegia, J. Rehabil. Med 49 (5) (2017) 369–377.
[4] S.J. Winser, et al., Measures of balance and falls risk prediction in people with Parkinson's disease: a systematic review of psychometric properties, Clin. Rehabil. 33 (12) (2019) 1949–1962.
[5] S. Tajali, et al., Predicting falls among patients with multiple sclerosis: Comparison of patient-reported outcomes and performance-based measures of lower extremity functions, Mult. Scler. Relat. Disord. 17 (2017) 69–74.
[6] M.K. Mak, M.M. Auyeung, The mini-BESTest can predict parkinsonian recurrent fallers: a 6-month prospective study, J. Rehabil. Med 45 (6) (2013) 565–571.
[7] J.N. Chee, et al., Influence of multiple sclerosis on spatiotemporal gait parameters: a systematic review and meta-regression, Arch. Phys. Med Rehabil. 102 (9) (2021) 1801–1815.
[8] S.M. Bruijn, et al., Assessing the stability of human locomotion: a review of current measures, J. R. Soc. Interface 10 (83) (2013) 20120999.
[9] R.P. Duncan, et al., Accuracy of fall prediction in Parkinson disease: six-month and 12-month prospective analyses, Park. Dis. 2012 (2012) 237673.
[10] L.R. Almeida, et al., Comparison of self-report and performance-based balance measures for predicting recurrent falls in people with parkinson disease: cohort study, Phys. Ther. 96 (7) (2016) 1074–1084.
[11] M.J. Boyce, et al., Validation of fear of falling and balance confidence assessment scales in persons with dystonia, J. Neurol. Phys. Ther. 41 (4) (2017) 239–244.
[12] S. An, et al., Discriminative and predictive validity of the short-form activities-specific balance confidence scale for predicting fall of stroke survivors, J. Phys. Ther. Sci. 29 (4) (2017) 716–721.
[13] R. Schniepp, et al., Increased gait variability is associated with the history of falls in patients with cerebellar ataxia, J. Neurol. 261 (1) (2014) 213–223.
[14] G. Chini, et al., Local stability of the trunk in patients with degenerative cerebellar ataxia during walking, Cerebellum 16 (1) (2017) 26–33.
[15] F. Reynard, et al., Could local dynamic stability serve as an early predictor of falls in patients with moderate neurological gait disorders? A reliability and comparison study in healthy individuals and in patients with paresis of the lower extremities, PLoS One 9 (6) (2014) e100550.
[16] A.T. Peebles, et al., Dynamic balance in persons with multiple sclerosis who have a falls history is altered compared to non-fallers and to healthy controls, J. Biomech. 63 (2017) 158–163.
[17] S. Tajali, et al., Impaired local dynamic stability during treadmill walking predicts future falls in patients with multiple sclerosis: a prospective cohort study, Clin. Biomech. (Bristol, Avon) 67 (2019) 197–201.
[18] E. Zwijgers, et al., Impaired foot placement strategy during walking in people with incomplete spinal cord injury, J. Neuroeng. Rehabil. 19 (1) (2022) 134.
[19] L. van de Venis, et al., Gait-Adaptability Training in People With Hereditary Spastic Paraplegia: A Randomized Clinical Trial, Neurorehabil Neural Repair 37 (1) (2023) 27–36.
[20] L. van de Venis, et al., Improving gait adaptability in patients with hereditary spastic paraplegia (Move-HSP): study protocol for a randomized controlled trial, Trials 22 (1) (2021) 32.
[21] D.M. Buchner, et al., Development of the common data base for the FICSIT trials, J. Am. Geriatr. Soc. 41 (3) (1993) 297–308.
[22] C. Peretz, et al., Assessing fear of falling: can a short version of the activities-specific balance confidence scale be useful? Mov. Disord. 21 (12) (2006) 2101–2105.
[23] F. Franchignoni, et al., Using psychometric techniques to improve the Balance Evaluation Systems Test: the mini-BESTest, J. Rehabil. Med 42 (4) (2010) 323–331.
[24] J.E. Graham, et al., Assessing walking speed in clinical research: a systematic review, J. Eval. Clin. Pr. 14 (4) (2008) 552–562.

[25] R. Schüle, et al., The spastic paraplegia rating scale (SPRS): a reliable and valid measure of disease severity, Neurology 67 (3) (2006) 430–434.
[26] F. Watson, et al., Use of the margin of stability to quantify stability in pathologic gait - a qualitative systematic review, BMC Musculoskelet. Disord. 22 (1) (2021) 597.
[27] S. Mehdizadeh, A robust method to estimate the largest Lyapunov exponent of noisy signals: A revision to the Rosenstein's algorithm, J. Biomech. 85 (2019) 84–91.
[28] R. Mofateh, et al., Effects of cognitive versus motor dual-task on spatiotemporal gait parameters in healthy controls and multiple sclerosis patients with and without fall history, Mult. Scler. Relat. Disord. 18 (2017) 8–14.
[29] A.L. Hof, M.G. Gazendam, W.E. Sinke, The condition for dynamic stability, J. Biomech. 38 (1) (2005) 1–8.
[30] Y. Wang, M. Srinivasan, Stepping in the direction of the fall: the next foot placement can be predicted from current upper body state in steady-state walking, Biol. Lett. 10 (9) (2014).
[31] S.A. England, K.P. Granata, The influence of gait speed on local dynamic stability of walking, Gait Posture 25 (2) (2007) 172–178.
[32] J.B. Dingwell, L.C. Marin, Kinematic variability and local dynamic stability of upper body motions when walking at different speeds, J. Biomech. 39 (3) (2006) 444–452.
[33] D.W.L., S. Hosmer, R.X. Sturdivant, Applied Logistic Regression. Wiley Series in Probability and Statistics, Third ed., Wiley, Hoboken, NJ, 2013.
[34] L. van de Venis, et al., Increased trunk movements in people with hereditary spastic paraplegia: do these involve balance correcting strategies? J. Neurol. 269 (8) (2022) 4264–4269.
[35] J. Nonnekes, et al., Neurological disorders of gait, balance and posture: a sign-based approach, Nat. Rev. Neurol. 14 (3) (2018) 183–189.
[36] M. Serrao, et al., Gait Patterns in Patients with Hereditary Spastic Paraparesis, PLoS One 11 (10) (2016) e0164623.
[37] M. Regensburger, et al., Inertial gait sensors to measure mobility and functioning in hereditary spastic paraplegia: a cross-sectional multicenter clinical study, Neurology 99 (10) (2022) e1079–e1089.
[38] Y. van Vugt, et al., Postural stability during gait for adults with hereditary spastic paraparesis, J. Biomech. 88 (2019) 12–17.
[39] P.C. Raffalt, et al., Economy, movement dynamics, and muscle activity of human walking at different speeds, Sci. Rep. 7 (2017) 43986.
[40] S.M. Bruijn, et al., Is slow walking more stable? J. Biomech. 42 (10) (2009) 1506–1512.
[41] A.L. Leddy, B.E. Crowner, G.M. Earhart, Utility of the mini-BESTest, BESTest, and BESTest sections for balance assessments in individuals with Parkinson disease, J. Neurol. Phys. Ther. 35 (2) (2011) 90–97.
[42] E. Duchesne, et al., Validity of the Mini-BESTest in adults with myotonic dystrophy type 1, Muscle Nerve 62 (1) (2020) 95–102.
[43] L.A.P. Viveiro, et al., Reliability, validity, and ability to identity fall status of the berg balance scale, balance evaluation systems test (BESTest), mini-BESTest, and Brief-BESTest in older adults who live in nursing homes, J. Geriatr. Phys. Ther. 42 (4) (2019) p. E45-e54.
[44] P.E. Magnani, et al., What is the best clinical assessment tool for identification of adults aged ≥80 years at high risk of falls? Physiotherapy 110 (2021) 63–69.
[45] M.J. Toebes, et al., Local dynamic stability and variability of gait are associated with fall history in elderly subjects, Gait Posture 36 (3) (2012) 527–531.
[46] L. Bizovska, et al., Local dynamic stability during gait for predicting falls in elderly people: a one-year prospective study, PLoS One 13 (5) (2018) e0197091.
[47] R.M. Pickering, et al., A meta-analysis of six prospective studies of falling in Parkinson's disease, Mov. Disord. 22 (13) (2007) 1892–1900.
[48] V. Jørgensen, et al., Falls and fear of falling predict future falls and related injuries in ambulatory individuals with spinal cord injury: a longitudinal observational study, J. Physiother. 63 (2) (2017) 108–113.