Clinical Neurophysiology 130 (2019) 1188–1195

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

Excessive short-latency stretch reflexes in the calf muscles do not cause postural instability in patients with hereditary spastic paraplegia

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ARTICLE INFO

Article history:
Accepted 2 May 2019
Available online 11 May 2019

Keywords:
Hereditary spastic paraplegia
Muscle spasticity
Postural balance

HIGHLIGHTS

- Balance is impaired in people with hereditary spastic paraplegia.
- Balance impairments are not related to enhanced short-latency stretch reflexes.
- Lack of suppression of muscle activity may primarily cause impaired balance.

ABSTRACT

Objective: To identify the role of hyperexcitable short-latency stretch reflexes (SLRs) on balance control in people with hereditary spastic paraplegia (PwHSP).
Methods: Sixteen PwHSP with triceps surae spasticity and 9 healthy control subjects were subjected to toes-up support-surface perturbations. EMG data were recorded from gastrocnemius, soleus and tibialis anterior. Furthermore, center-of-mass trajectories were recorded.
Results: PwHSP were less able to withstand the perturbations. Triceps surae SLRs (40–80 ms post perturbation) in PwHSP were increased compared to healthy subjects. Furthermore, a sustained triceps surae EMG activity at 220–320 ms post perturbation was observed in PwHSP, whereas control subjects demonstrated suppression of triceps surae activity. Center of mass trajectories started to diverge between PwHSP and controls only after ~500 ms, with greater excursions being observed in the PwHSP.
Conclusions: The present results confirm that balance control is impaired in PwHSP. However, the late instant of center of mass divergence argues against a direct, causative role of hyperexcitable SLRs in the triceps surae.
Significance: We postulate that enhanced short-latency stretch reflexes of the triceps surae do not underlie poor balance control in PwHSP. Instead, we suggest the lack of suppression of later triceps surae activity to be the main cause.

1. Introduction

Hereditary spastic paraplegia (HSP) describes a heterogeneous group of neurodegenerative disorders characterized by slowly progressive leg muscle spasticity and muscle weakness (McDermott et al., 2000, Salinas et al., 2008, Schule and Schols, 2011) The main neuropathological feature is axonal degeneration of the longest descending and ascending nerve fibres (i.e. crossed and uncrossed corticospinal tracts to the legs, fasciculus gracilis fibers and, to a lesser extent, spinocerebellar fibers (McDermott et al., 2000)). HSP can be phenotypically classified into pure and complicated forms. Complicated phenotypes include symptoms such as dementia, ataxia and peripheral neuropathy, in addition to leg muscle spasticity. In contrast, people with pure HSP (PwHSP) mainly experience lower limb spasticity with relatively preserved muscle strength, motor selectivity and proprioception (Nielsen et al., 1998a, McDermott et al., 2000, Klebe et al., 2004). The spasticity in the lower extremities causes the typical gait abnormalities observed in PwHSP, which include forefoot landing, foot drag

Abbreviations: HSP, hereditary spastic paraplegia; PwHSP, people with hereditary spastic paraplegia; SLR, short latency response; MLR, medium latency response; LLR, long latency response; CoM, center of mass; FAC, Functional Ambulation Categories; MAS, Modified Ashworth Scale; GM, gastrocnemius; SOL, soleus; TA, tibialis anterior; EMG, electromyography.

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https://doi.org/10.1016/j.clinph.2019.05.005
1388-2457/

during swing, and increased hip adduction ('scissoring' gait). Furthermore, it becomes increasingly evident that PwHSP also suffer from impaired balance control (e.g. Nardone et al. (2001), de Niet et al. (2013), Nonnekes et al. (2013), de Niet et al. (2015)). However, the mechanism underlying these balance impairments – and in particular the role of leg muscle spasticity – is yet poorly understood.

Spasticity is commonly defined as the velocity-dependent hyperexcitability of spinal stretch reflexes (Lance, 1990). Nardone et al. (2001) have shown that patients suffering from calf muscle spasticity indeed exhibit exaggerated short latency stretch reflexes (SLR) in the triceps surae following a sudden rotation in toes-up direction, imposed by a moveable platform (inducing ankle dorsiflexion movements). Toes-up rotations induce backward falls. To overcome this perturbation, the tibialis anterior muscle has to generate a corrective ankle dorsiflexion torque to pull the center of mass in the forward direction. Muscle activity of the antagonist muscles – i.e. the triceps surae – may thus be detrimental for balance recovery following toes-up perturbations. An earlier study of our group (de Niet et al., 2013) suggested a detrimental effect of triceps surae spasticity on postural stability. The maximal magnitude of rotational toes-up perturbations that PwHSP could sustain without stepping (i.e. stepping threshold) was associated with clinical scores of triceps surae spasticity; patients with more severe spasticity had lower stepping thresholds. The latter result may seem to concur with a destabilizing effect of hyperexcitable stretch reflexes of the triceps surae. However, it is questionable whether the SLR can generate sufficiently large torques at the ankle joint to induce a loss of balance (Jacobs and Horak, 2007). Some previous studies suggested that increased SLRs as a result of spasticity contributed to functional impairments in both balance and gait (Crenna, 1998, Nielsen et al., 1998b, Sinkjaer et al., 1999, Lamontagne et al., 2001, de Niet et al., 2013), whereas other studies suggested there was no evident functional consequence of an increased SLR (Nardone et al., 2001, van der Krogt et al., 2010, de Niet et al., 2011). Hence, is it important to further investigate the effects of excessive SLRs on balance control. Furthermore, it cannot be excluded that later phases of the postural response may also be defective in PwHSP.

The purpose of the current study was to gain further insight into the mechanisms underlying impaired balance control in PwHSP. To address this aim, toes-up support-surface balance perturbations at several intensities, imposed by a rotational platform, were applied in PwHSP and healthy control subjects. Previous research from our lab showed that after such toes-up perturbations, PwHSP overall had lower success rates, compared to healthy controls (de Niet et al., 2015). However, to provide insight in the underlying mechanisms, success rates for different intensities, electromyographic (EMG) responses from the triceps surae, and the time course of center-of-mass (CoM) excursions and velocities following perturbations were investigated in the current study. The instant where CoM trajectories start to diverge between PwHSP and controls provides crucial information on the causal role of hyperexcitable stretch reflexes in the impaired ability of PwHSP to withstand these toes-up perturbations. We hypothesized that exaggerated SLRs in the triceps surae of PwHSP would lead to difficulties in sustaining toes-up perturbations. This would be reflected by an early divergence (<200 ms post perturbation) of their CoM trajectories in PwHSP compared to those of control subjects.

2. Methods

2.1. Study design

For addressing the present research question, we used the baseline data as obtained in the FEBOCH-I study (de Niet et al., 2015). The FEBOCH-I study aimed to assess the effects of botulinum toxin injections in the triceps surae, with success rates of balance recovery to multidirectional translational and rotational perturbations as secondary outcomes. These were assessed at baseline and at 4 and 18 weeks post intervention. The baseline assessment also included EMG measurements, which allowed us to conduct this additional mechanistic study on the role of excessive stretch reflexes in recovering balance following rotational 'toes-up' perturbations.

2.2. Participants

Participants were recruited from all symptomatic PwHSP who visited the Rehabilitation and/or Neurology outpatient clinics of our university hospital during a period of one year. In addition, active recruitment took place through advertisements and oral presentations for the national patient council (Spierziekten Nederland). PwHSP could be included if they were (1) having autosomal dominant pure HSP (either genetically proven or based on family history), (2) having clinical symptoms of spasticity (e.g. clonus, stiffness, muscle cramps pain), and (3) being a community ambulator (Functional Ambulation Categories (FAC) score 5 (Holden et al., 1984)). Exclusion criteria were (1) Modified Ashworth Scale (MAS) score of the calf muscle with the knee flexed or extended greater than 2 (Bohannon and Smith, 1987), (2) passive ankle range of motion with an extended knee less than 10° dorsiflexion, (3) leg muscle strength (both calf and tibialis anterior muscles) lower than 4 on the Medical Research Council (MRC) scale (Medical Research, 1981), and (4) motor selectivity lower than stage 5 of the Brunnström stages, all on either side of the body (Fugl-Meyer et al., 1975). After screening 32 PwHSP, 16 PwHSP met the inclusion criteria and were included in this study. Demographics and clinical characteristics of the included PwHSP are listed in Table 1. In addition, 9 healthy controls of similar age were recruited. The study was approved by the regional medical ethics committee and was conducted in accordance with the Declaration of Helsinki. All subjects gave written informed consent before the experimental procedures.

2.3. Balance assessment

Subjects stood barefoot on a moveable platform with their knees extended and their feet at shoulder width. They wore a safety harness, which was attached to the ceiling, and prevented them from falling. The platform imposed rotational (toes-up and toes-down) and translational (forward and backward) perturbations. Perturbations were applied at four intensity levels (3°, 5°, 7° and 9° rotation; translations at 0.25, 0.50, 0.75 and 1.00 $m{\cdot}s^{-2}$). For detailed specifications of the perturbations and the platform, see de Niet et al. (2013).

The protocol consisted of four familiarization trials of each of the four perturbations at the lowest intensity (i.e. 3° rotation or translation at 0.25 $m{\cdot}s^{-2}$) to familiarize the participants with the experimental setup. Thereafter, a total number of 64 perturbations were imposed in random order with four perturbations at each intensity level for each type of perturbation (e.g. 4 types × 4 intensities × 4 repetitions). Participants were instructed to respond to the perturbations without stepping or grabbing for support. For each trial it was determined whether the participant was successful in recovering balance with the requested feet-in-place response. This resulted in a success rate (proportions of successfully performed trials) for each type of perturbation. In this paper, only the results for the toes-up rotations are reported, as those perturbations applied a rapid stretch to the triceps surae and were thus related to stretch-related activity.

Table 1
Demographic and clinical characteristics of patients with autosomal dominant hereditary spastic paraplegia and control subjects.

	HSP	Healthy controls
N	16	9
Age (mean ± SD)	48.8 ± 12.8	47.3 ± 11.8
Gender (male/female)	12/4	6/3
Genetic diagnosis		
SPG-4	9	
SPG-3A	1	
SPG-8	1	
Unknown genotype	5	
MAS calf muscle‡		
SOL	1 (n = 6); 2 (n = 10)	
GM	1 (n = 8); 2 (n = 8)	
MRC calf muscle‡	5 (n = 10); 4 (n = 6)	
MRC dorsiflexion‡	5 (n = 16)	
Vibration sense (mean ± SD)*	4.0 ± 2.0	

HSP, Hereditary Spastic Paraplegia; MAS, Modified Ashworth Scale; MRC, Medical Research Council.
‡ Left and right leg scored equally.
* Assessed with Rydel-Seiffer tuning fork.

2.4. Kinematics and EMG

Three-dimensional kinematic data of the lower limbs and the trunk were collected using a motion capture system (Vicon Motion Systems®, Oxford, UK) at a sample frequency of 100 Hz. Twenty-one reflective markers were placed on the trunk and lower limbs according to the full-body PlugInGait configuration (Vicon Motion Systems®, Oxford, UK). Furthermore, bilateral muscle activity was recorded by surface electromyography at a sample frequency of 1000 Hz from the medial head of the gastrocnemius (GM), soleus (SOL) and tibialis anterior (TA) muscles with electrodes (Ag-AgCl, ARBO ECG electrodes, Tyco Healthcare, Neustadt, Germany) placed according to SENIAM guidelines.

2.5. Data processing and analysis

The marker data were processed using the PlugInGait model in Vicon Nexus (Vicon Motion Systems®, Oxford, UK; (Delp et al., 2007)). Based on the hip markers and anthropologic data, the Vicon system determined a virtual CoM according to the PlugInGait model. Subsequently, CoM position data were low-pass filtered at 10 Hz (2nd order zero-lag Butterworth filter) and CoM velocity data were derived from CoM position data. EMG signals were band-pass filtered (10–499 Hz, 2nd order zero-lag Butterworth filter), rectified and low-pass filtered with 100 Hz. Thereafter, the EMG signal was normalized (i.e. expressed as a percentage of the background EMG activity averaged over 100 ms prior to onset perturbation). For each subject and perturbation intensity, kinematic and EMG data were ensemble averaged across trials and across the left and right leg. We determined the mean (normalized) EMG amplitude over four time windows following the start of the perturbation; 40–80 ms (short-latency response, SLR), 80–120 ms (medium latency response, MLR), 120–220 ms (long latency responses, LLR) and 220–320 ms (post-LLR, (Gottlieb and Agarwal, 1979, Sinkjaer et al., 1999)).

2.6. Statistical analysis

The success rates of balance recovery without stepping were compared between the PwHSP and controls using a factorial ANOVA with *group* as between-subjects factor and *perturbation intensity* as within-subjects factor. Post-hoc analysis involved bonferroni-corrected independent t-tests.

The (normalized) EMG amplitudes were compared between the PwHSP and controls for each time window of interest (i.e. SLR, MLR, LLR and post-LLR) by means of a repeated-measures ANOVA with *group* as between-subjects factor and *perturbation intensity* as within-subjects factor. An independent students t-test was used to compare background activity between PwHSP and controls. Finally, to determine the instant that CoM trajectories started to diverge between PwHSP and controls, we compared the CoM excursions and velocities for each intensity of perturbation using consecutive one-sided independent t-tests at time intervals of 10 ms following the onset of the perturbation. The α-level was set at 0.05 for all analyses.

3. Results

For the most severely affected PwHSP (n = 4) it was too demanding – both in terms of fatigue and safety – to undergo the total number of perturbations (64 trials). Therefore, the perturbations at the highest intensity of each type were omitted, leaving 48 perturbations for these participants. In the remainder of the paper, the EMG results for the three levels of perturbation intensities that could be collected in all PwHSP will be reported. Yet, subgroup analysis for the 12 PwHSP who underwent the full number of perturbations yielded a similar pattern of results (Supplementary Fig. S1).

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.clinph.2019.05.005.

3.1. Success rates following toes-up perturbations

PwHSP were less capable of withstanding toes-up perturbations without stepping or grabbing for support (main effect of *group*, $t(23) = 5.439$, $p < 0.001$). PwHSP exhibited a large decrement in performance at higher perturbation intensities, whereas the controls barely failed to recover balance at all (*group* * *intensity*, $F(3,69) = 10.141$, $p < 0.001$, Fig. 1). Post-hoc tests yielded significant differences between the groups at perturbations of 5° ($t(23) = 4.000$, $p = 0.001$), 7° ($t(23) = 4.251$), $p < 0.001$), and 9° ($t(23) = 8.326$, $p < 0.001$), whereas success rates at perturbations of 3° did not differ ($t(23) = 1.661$, $p < 0.001$).

3.2. EMG responses – between-group differences

Mean SOL, GM and TA EMG traces of a representative control subject and participant with HSP during toes-up perturbations

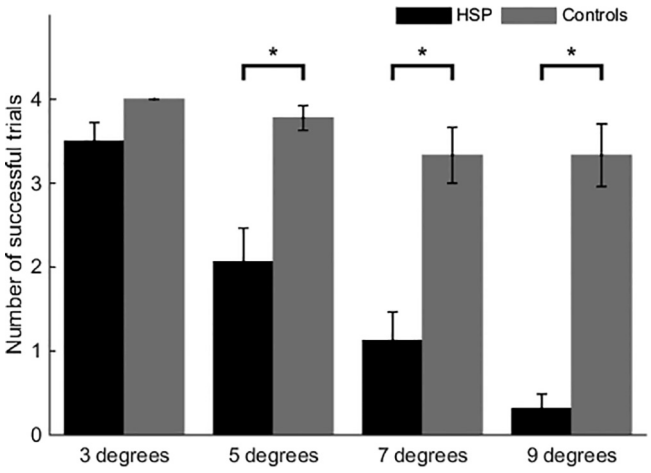

Fig. 1. Mean success rates (SD) of PwHSP (black) and control subjects (grey) at the three intensities of rotational toes-up perturbations. Asterisks mark significant differences between the groups.

are shown in Fig. 2. All EMG results of each muscle per time interval are presented in Table 2. The average background activity prior to perturbation was not significantly different between PwHSP and controls in GM ($t(9.6) = 2.2124$, $p = 0.052$), SOL ($t(23) = 0.440$, $p = 0.664$), or TA ($t(22.2) = -1.509$, $p = 0.145$).

In Fig. 3, the SOL, GM and TA responses (normalized to background activity) following perturbations are shown for PwHSP and controls. SLR amplitudes were larger in PwHSP than in controls in both the SOL (Fig. 3a, $F(1,23) = 4.516$, $p = 0.045$) and GM muscle (Fig. 3b, $F(1,23) = 4.847$, $p = 0.038$). In contrast, the response amplitudes in both the MLR and LLR time windows did not differ between the groups in either calf muscle. In the post-LLR time window, however, the PwHSP demonstrated greater muscle activity again compared to controls in GM ($F(1,23) = 7.429$, $p = 0.012$) and SOL ($F(1,23) = 4.394$, $p = 0.047$). The response amplitudes in the TA muscle were not different between the groups in any of the time windows (Fig. 3c).

3.3. EMG responses – effects of perturbation intensity

In the SOL, no effects of perturbation intensity were shown in any of the response amplitudes. For the GM, greater post-LLR amplitudes were observed at higher perturbation intensities ($F(2,46) = 6.190$, $p = 0.004$), whereas there was no perturbation intensity effect in SLR, MLR and LLR response amplitudes. For TA, post-LLR response amplitudes increased with increasing perturbation intensities ($F(1.552,35.675) = 8.778$, $p = 0.002$), which effect was not present in the other TA response windows. None of the *intensity * group* interaction effects reached significance.

3.4. Center-of-mass displacement

The averaged CoM displacements and velocities of the groups are depicted at each intensity of perturbation (Fig. 4). The CoM trajectories were very similar between individual participants and between the groups in the first ~ 300 ms post perturbation. From ~ 500 ms onwards, the variability in trajectories between subjects increased considerably, which was particularly evident in the HSP group. As shown in Fig. 4a, no point of divergence of CoM excursions could be identified up to 1000 ms for perturbations of 3°. The statistical points of divergence between the CoM excursions of both groups were at 520 ms ($t(23) = 1.777$, $p = 0.044$), 490 ms ($t(23) = 1.785$, $p = 0.043$) and 460 ms ($t(19) = 1.767$, $p = 0.047$) for perturbations of 5°,7° and 9°, as shown in Fig. 4c, 4e and 4 g respectively. The statistical points of divergence between the CoM velocities of both groups were detected at

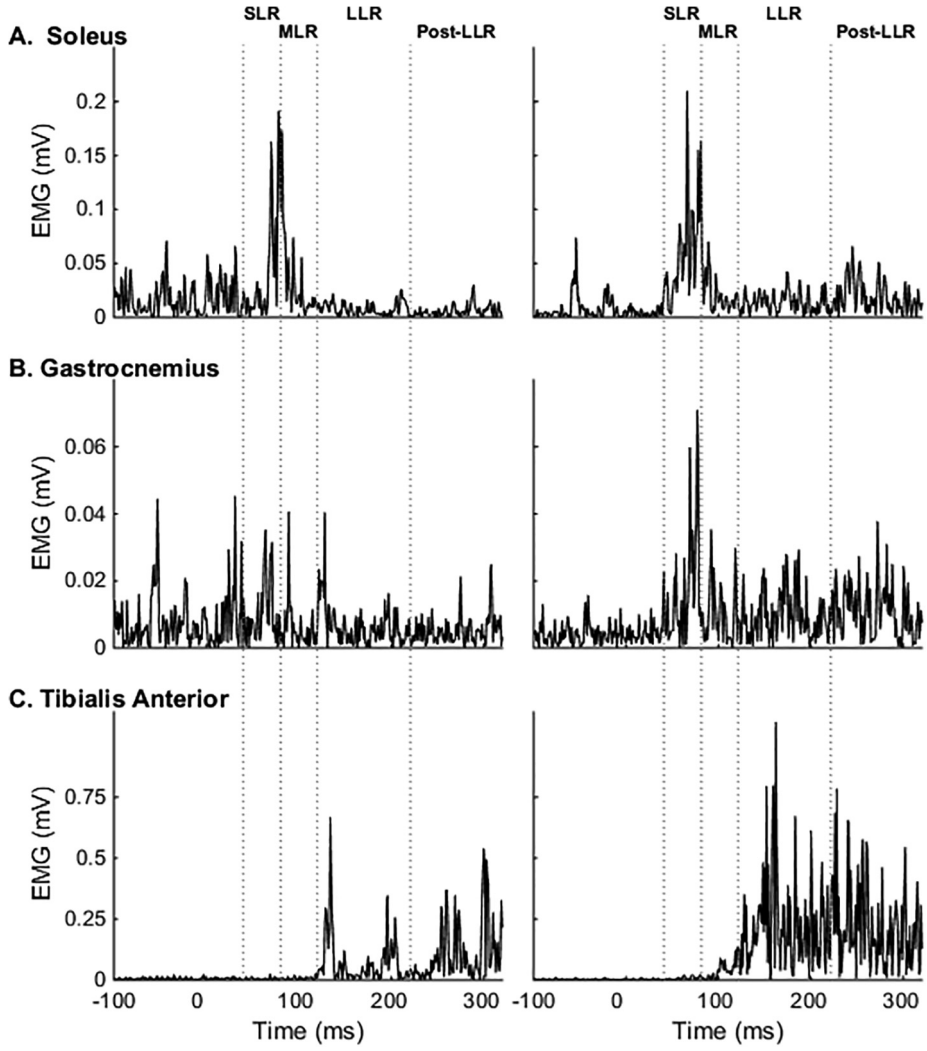

Fig. 2. Representative rectified raw EMG traces of a control subject (left column) and an participant with HSP (right column) after a 7° toes-up perturbation. Time zero is the time of the perturbation onset. Note that the participant with HSP has higher SLR and post-LLR responses in SOL and GM compared to the control subject. SOL, Soleus; GM, Gastrocnemius.

Table 2
EMG outcome measures per time window for PwHSP and healthy controls.

Muscle	Time window	Group	Mean percentage EMG from background ± SD 3°	5°	7°	Intensity effect	Group effect
SOL	SLR	HSP	227 ± 110	245 ± 153	220 ± 61	F(2,46) = 0.463,	**F(1,23) = 4.516,**
		Control	136 ± 31	139 ± 29	176 ± 59	p = 0.632	**p = 0.045**
	MLR	HSP	204 ± 61	233 ± 91	233 ± 76	F(2,46) = 1.470,	F(1,23) = 0.014,
		Control	218 ± 146	197 ± 92	243 ± 139	p = 0.241	p = 0.907
	LLR	HSP	121 ± 61	167 ± 87	162 ± 73	F(2,46) = 2.072,	F(1,23) = 0.080,
		Control	147 ± 104	152 ± 104	176 ± 107	p = 0.138	p = 0.780
	Post-LLR	HSP	104 ± 52	107 ± 56	98 ± 44	F(2,46) = 0.284,	**F(1,23) = 4.394,**
		Control	68 ± 47	58 ± 31	67 ± 34	p = 0.754	**p = 0.047**
GM	SLR	HSP	191 ± 47	204 ± 69	254 ± 178	F(1.427,32.818) = 3.191,	**F(1,23) = 4.847,**
		Control	127 ± 51	138 ± 43	178 ± 92	p = 0.069*	**p = 0.038**
	MLR	HSP	181 ± 47	215 ± 114	279 ± 241	F(1.353,31.123) = 3.311,	F(1,23) = 0.014,
		Control	206 ± 92	219 ± 122	268 ± 172	p = 0.067*	p = 0.906
	LLR	HSP	188 ± 115	277 ± 206	306 ± 244	F(1.299,29.875) = 2.986,	F(1,23) = 0.583,
		Control	179 ± 85	174 ± 104	277 ± 294	p = 0.085*	p = 0.453
	Post-LLR	HSP	114 ± 45	127 ± 53	146 ± 66	**F(2,46) = 6.190,**	**F(1,23) = 7.429,**
		Control	71 ± 48	65 ± 36	87 ± 54	**p = 0.004**	**p = 0.012**
TA	SLR	HSP	116 ± 23	117 ± 35	121 ± 41	F(1.553,35.710) = 0.362,	F(1,23) = 3.458,
		Control	111 ± 20	97 ± 13	100 ± 17	p = 0.645*	p = 0.076
	MLR	HSP	265 ± 261	359 ± 468	482 ± 756	F(1.541,35.448) = 0.747,	F(1,23) = 0.449,
		Control	228 ± 111	333 ± 481	232 ± 130	p = 0.448*	p = 0.510
	LLR	HSP	1196 ± 1175	1237 ± 1356	1455 ± 1666	F(1.407,32.369) = 1.298,	F(1,23) = 0.094,
		Control	1402 ± 750	1223 ± 762	1669 ± 658	p = 0.277*	p = 0.762
	Post-LLR	HSP	1632 ± 1025	1899 ± 1112	2207 ± 1385	**F(1.551,35.675) = 8.778,**	F(1,23) = 0.193,
		Control	1731 ± 937	1859 ± 1171	2714 ± 1214	**p = 0.002***	p = 0.665

MLR, medium-latency reflex; LLR, long-latency reflex.
Bold values indicate statistical significance.
* Sphericity not assumed, Greenhouse-Geisser test used. SOL, Soleus; GM, Gastrocnemius; TA, Tibialis anterior; SLR, short-latency reflex.

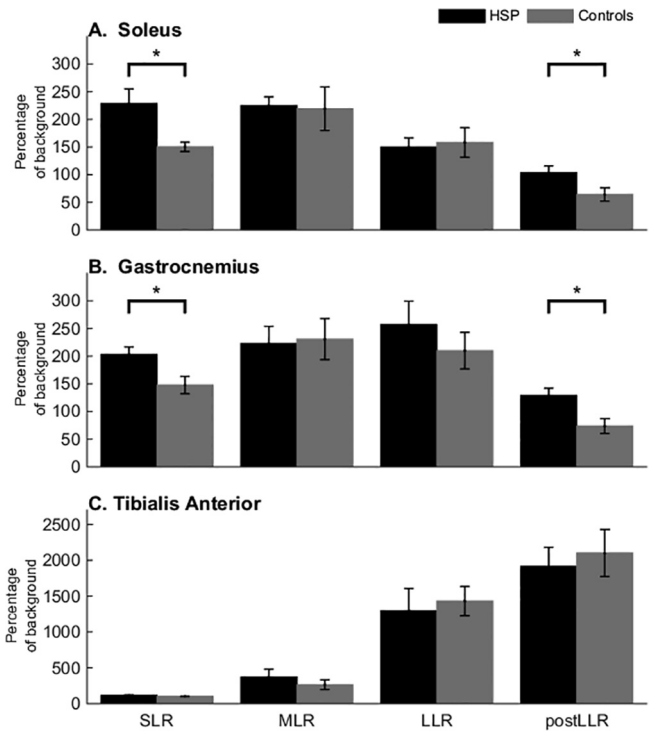

Fig. 3. Overall EMG activity (averaged over 3 intensities) for each post-perturbation time window in (A) SOL, (B) GM and (C) TA. Black bars represent data of PwHSP, grey bars of the control group. Asterisks mark significant differences between the groups. SOL, Soleus; GM, Gastrocnemius; TA, Tibialis anterior.

430 ms (t(23) = 1.793, p = 0.043) , 420 ms (t(23) = 2.012, p = 0.028), 400 ms (t(23) = 1.857, p = 0.038) and 410 ms (t(19) = 1.780, p = 0.046) for the 3°, 5°, 7° and 9° perturbations, as shown in Fig. 4b, 4d, 4f and 4 h, respectively.

4. Discussion

The main aim of this study was to identify whether hyperexcitability of triceps surae short-latency stretch reflexes (SLRs) is a key determinant of the poor balance control in PwHSP in response to toes-up support-surface rotations. In line with their pronounced leg muscle spasticity, we indeed observed increased SLRs in the triceps surae of the PwHSP compared to healthy controls. The great difficulty that the PwHSP experienced in sustaining the perturbations was evident from their lower success rates and greater CoM excursions and velocities in comparison to the controls. The PwHSP also demonstrated enhanced triceps surae activity in the post long-latency reflex (LLR) time window (220–320 ms) compared to the controls, whereas the MLR and LLR response amplitudes did not differ. For TA activity, no differences between the groups were found in any of the time windows.

The present results confirm previous findings of impaired balance control and increased short-latency stretch reflexes in spastic triceps surae upon sudden toes-up support-surface rotations (Nardone et al., 2001, de Niet et al., 2013). Yet, studies on the significance of leg muscle spasticity for defective balance control are yet sparse and the results disparate. This lack of knowledge might be due to the fact that spasticity in patients with upper motor neuron syndromes often coexists with other impairments (e.g. paresis, sensory loss, contractures, involvement of other structures relevant for balance control). HSP, however, is mainly characterized by spasticity, whereas muscle strength, somatosensation and range of joint motion are relatively well preserved. HSP thus provides a 'naturalistic model' for studying how spasticity contributes to impaired balance control. Our study adds to the existing knowledge on the impact of leg muscle spasticity in balance control as, contrary to our hypothesis, the results demonstrate that there does not seem to be a direct, causative relationship between hyperexcitable SLRs in triceps surae and poor balance performance. Furthermore, we here report a yet unidentified abnormality in the spastic triceps surae

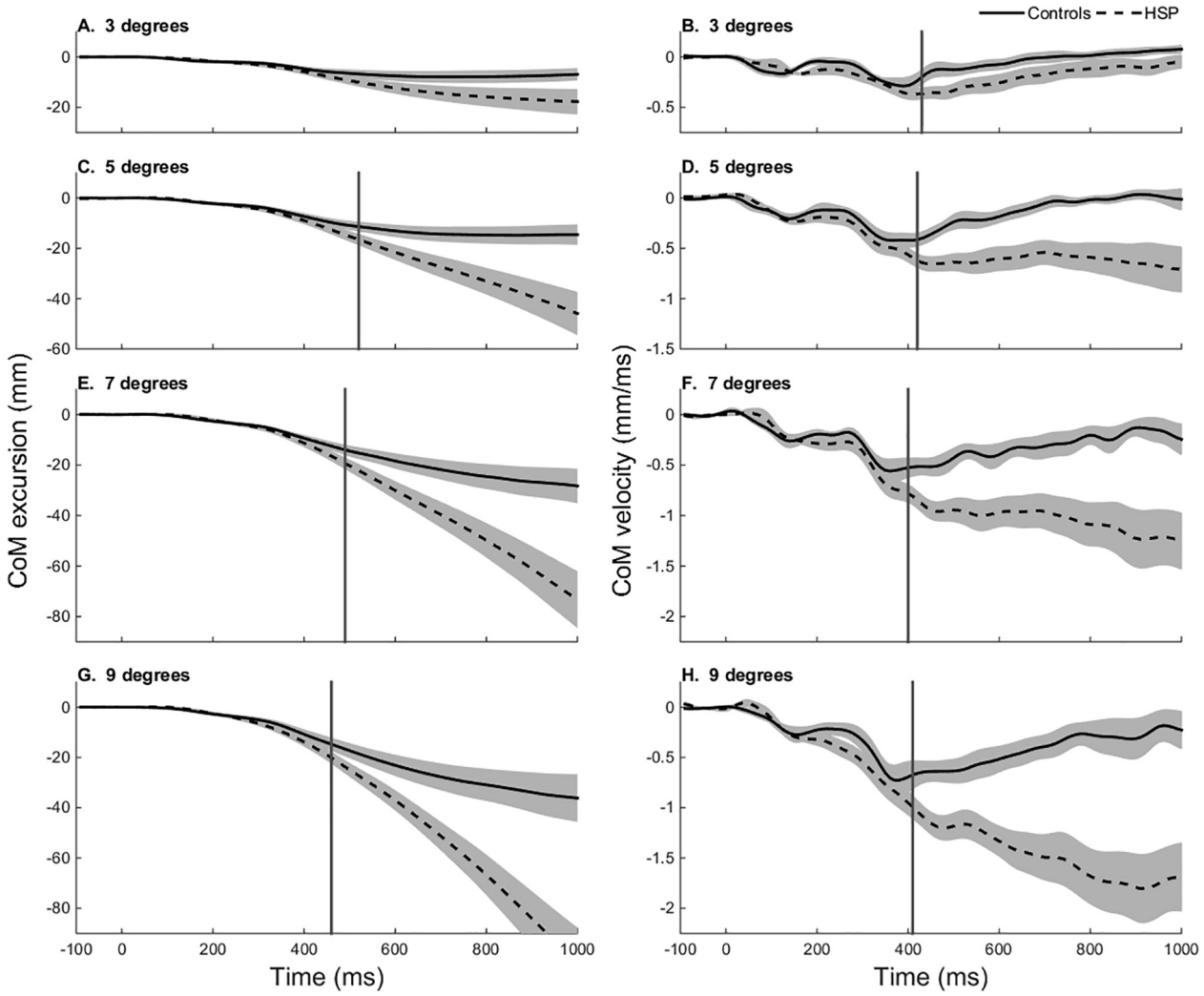

Fig. 4. Average CoM excursion (left) and CoM velocity (right) patterns of PwHSP (dashed line) and controls (solid line) for (A, B) 3° perturbations, (C, D) 5°, (D, E) 7° and (F, G) 9°. The onset of perturbation is at 0 ms. Points of divergence based on significance of independent t-test are marked with grey solid vertical line. Com, Center of mass.

(i.e. sustained activity in the post-LLR window), which potential significance will be further eluded on.

The PwHSP had more difficulties to recover from the perturbations without stepping than the control subjects. Indeed, the PwHSP demonstrated greater CoM excursions and velocities compared to controls, which became apparent in the statistical analyses of CoM velocities at 400–430 ms post perturbation. People recover from "toes-up" rotational balance perturbations by generating corrective ankle dorsiflexion torques, through MLR and LLR responses at onset latencies of ~ 100–115 ms (Allum et al., 2002, Campbell et al., 2009). In a previous study on toes-up rotational balance perturbations in people with leg muscle weakness, it was demonstrated that distal weakness (i.e. a reduced capacity to generate large corrective torques) resulted in evident divergence of COM velocity from that of healthy subjects at ~ 225 ms post perturbation (Horlings et al., 2009). These results point at a time lag of ~ 110–125 ms between (differences in) EMG activity and (differences in) COM velocity. Therefore, it seems unlikely that increased SLRs in the (spastic) triceps surae have a direct, causal relation with the larger CoM excursions in PwHSP. Conversely, the relatively late instants of divergence between CoM trajectories of PwHSP and healthy controls more likely correspond with the enhanced triceps surae activity that was observed in our PwHSP at 220–320 ms post perturbations. In this (post-LLR) time window, the PwHSP generally demonstrated sustained triceps surae activity, whereas control subjects showed strong inhibition of these muscles (i.e. below background activity levels). As TA activity has to overcome the triceps surae activity to recover balance following toes-up perturbations, the sustained triceps surae (i.e. antagonist) activity must be considered detrimental for balance control.

The observation of sustained triceps surae activity in the post-LLR time window in the PwHSP was an unexpected finding, and the mechanisms underlying this lack of inhibition can only be speculated upon. One suggestion may be related to the degeneration of the long descending tracts as a key neuropathological feature of the disease (McDermott et al., 2000, Salinas et al., 2008, Schule and Schols, 2011). Dendrites of motoneurons have voltage dependent channels that provide the capacity to generate persistent inward currents. It has been demonstrated that, due to a lack of descending input, large persistent inward currents make the spinal cord hyperexcitable, which may lead to a self-sustained firing of motoneurons after muscle activation (Heckmann et al., 2005, Nielsen et al., 2007, Li and Francisco, 2015). The evoked activity post perturbation in the spastic triceps surae of PwHSP may cause a self-sustained firing of motoneurons, causing further prolongation of muscle responses. An alternative (and not mutually exclusive) suggestion for the prolonged triceps surae activity could be a lack of reciprocal inhibition in the lower leg muscles, which

has previously been demonstrated in PwHSP (Crone et al., 2004). Following toes-up perturbations, activity of TA muscles is required for maintaining balance. This mechanism normally leads to inhibition of the triceps surae (which we indeed observed in the healthy controls), but may have been defective in the PwHSP. A different notion is a possible neurophysiological relationship between excessive SLRs and muscle activity during the post-LLR window, but the fact that we found no group differences in the MLR and LLR time windows seems to argue against this possibility. It must be mentioned, though, that all these suggested explanations for the (newly identified) sustained triceps surae activity remain speculative, as our study was not designed to elucidate the neural processes involved.

In addition to the results on triceps surae activity, the lack of between-group differences in tibialis anterior activity may be considered as another HSP-related abnormality. Given the enhanced triceps surae activity in the PwHSP compared to controls, greater activity of TA – as the agonist muscle for recovering balance – would be expected to compensate for that. However, the absence of differences in TA activity suggests that the PwHSP had difficulties recruiting such compensatory activity (and thus corrective torques), which may also have contributed to their lower recovery success rates. In the present group of PwHSP, however, muscle strength of ankle dorsiflexors was normal (MRC = 5; see Table 1), which suggests that the rate of TA recruitment may be more of a problem than its absolute strength.

Our results suggest that sustained muscle activity in the post-LLR window may help explain the observed difficulties that the PwHSP experienced in recovering from toes-up perturbations. Although rotational perturbations do not occur often in daily life, sustained muscle activity may also compromise other postural tasks for which quick inhibition is important. This could be the case for larger balance perturbations that necessitate stepping to recover. Any perturbation to balance evokes an automated postural response, which leads to bilateral activation of leg muscles for counteracting the perturbation-induced CoM excursions. When the CoM excursions exceed the boundaries of the base of support and a compensatory step is needed to recover, making this step requires rapid inhibition of postural muscle activity in the stepping leg. Future research should identify which neural mechanism underlies the sustained triceps surae activity in PwHSP, and whether this sustained activity may indeed contribute to poor balance control.

A limitation of this exploratory study is that the group of PwHSP was relatively small (inherent to the rarity of the disease) and heterogeneous (despite our restriction to 'pure' HSP phenotypes). We, therefore, chose not to adjust the statistical criterion for multiple testing, as this would introduce a substantial risk of type II (false-negative) errors. Although multiple testing at uncorrected alpha levels bears a risk of type I (false-positive) errors, we would like to emphasize that we observed a consistent pattern of significant between-group differences in the SLR and post-LLR time-windows for both the soleus and gastrocnemius muscles. In addition, the direction of this effect in the SLR window was coherent with the underlying pathophysiological mechanism and with results from a previous study in HSP (Nardone et al., 2001). Hence, it is deemed unlikely that the present results represent false-positive outcomes. Another limitation is that we did not measure corrective ankle torques. Such data would have allowed us to appreciate the mechanical effects of the HSP-related differences in triceps surae activity more directly. Furthermore, it remains difficult to provide conclusive evidence for cause-and-effect relationships from discrete perturbations due to the complex interplay of the various systems involved in balance control. Interestingly, a powerful new computational method (closed-loop system identification technique) has recently been proposed to identify such causal relationships from imposed continuous mechanical perturbations and recorded responses at the level of EMG, joint torques and body sway (Pasma et al., 2014). The application of this method may provide further insight into the mechanisms underlying defective balance control in PwHSP.

5. Conclusion

The present results confirm that balance control is impaired in PwHSP. These balance impairments, however, do not seem to be directly related to hyperexcitable short-latency stretch reflexes of spastic triceps surae muscles. Rather, they seem to be due to lack of triceps surae activity suppression in the post long-latency reflex time window. Further research into the neural underpinnings of defective balance control in HSP should particularly focus on the possible role of impaired reciprocal inhibition and/or enhanced (self-sustained) firing of the motoneurons that innervate the triceps surae.

Funding

Unrestricted grant from Ipsen Farmaceutica BV in the Netherlands.

Declaration of Competing Interest

None of the authors have potential conflicts of interest to be disclosed.

Acknowledgements

Alexander Geurts was supported by an unrestricted grant from Ipsen Farmaceutica BV in the Netherlands. The company was not involved in the collection, analysis and interpretation of data and in the writing of the manuscript.

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