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Neuromuscular control during gait in people with haemophilic arthropathy

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Introduction: Effects of haemophilic arthropathy on neuromuscular control during gait are currently unknown.

Aims: (a) To assess how haemophilic arthropathy affects the complexity of neuromuscular control during gait; (b) To investigate the relationship between complexity of neuromuscular control and joint impairment.

Methods: Thirteen control subjects (CG) walked overground at their preferred and a slow velocity and thirteen people with haemophilic arthropathy (PWHA) walking at their preferred velocity. Surface electromyography (EMG) was collected from eleven leg muscles. Electromyography variance explained by muscle synergies (sets of co-activated muscles that can be recruited by a single signal) was calculated by the total variance accounted (tVAF). Three measures were used to evaluate complexity of neuromuscular control: (a) the number of synergies required for tVAF > 90%, (b) tVAF as a function of the number of muscle synergies, and (c) the dynamic motor control index (Walk-DMC). Impairment of ankle and knee joints was determined by the Haemophilia Joint Health Score (HJHS).

Results: The same number of the muscle synergies was found for each group ($P > 0.05$). For both walking velocities tested, tVAF1 was higher in PHWA ($P < 0.05$). The Walk-DMC of PWHA was lower than that of the CG for both walking velocities ($P < 0.05$). For PWHA, no significant correlation was found between HJHS (sum knee and ankle) and Walk-DMC index ($r = -0.32$, $P = 0.28$).

Conclusions: These results indicate differences between PWHA and CG in the neuromuscular control of gait. The Walk-DMC and tVAF1 may be useful measures to assess changes in neuromuscular control in response to treatment.

KEYWORDS
ankle joint, haemophilia, knee joint, muscle synergy, neuromuscular control, surface electromyography

1 | INTRODUCTION

Haemophilic arthropathy is the result of repetitive intra-articular bleeding and synovial inflammation.[1] In the lower limb, haemophilic arthropathy commonly affects the range of motion of the knee and ankle joints and has also an impact on muscle size, muscle force capacity and proprioception.[1,2] While the interest in the musculoskeletal properties and biomechanics of movement of people with haemophilic arthropathy (PWHA) has recently increased,[3,5-7] the effects of haemophilic arthropathy on neuromuscular control during gait have not been investigated.

Instead of focusing on the activity patterns of individual muscles, the neuromuscular control of motor tasks can be described by muscle synergies,[8-10] A muscle synergy is a group of muscles that are recruited simultaneously (ie co-activated) with distinct relative levels of activation. The central nervous system (CNS) is presumed to produce movements not by activating individual muscles, but by activating muscle synergies.[8-10] In healthy individuals, it has been shown that a large part (>90%) of the variance in muscle activity during gait can be described by a limited number (4-5) of muscle synergies.[11,12]

The same approach has been applied in several neurological diseases (ie cerebral palsy, Parkinson, stroke and incomplete spinal cord injury). Patients were found to use a lower number of muscle synergies and altered structure of the synergies, which was related to functional and clinical assessments.[13-16] A lower number of synergies is interpreted as a more simplified (ie decreased complexity) control by the CNS. When applied in musculoskeletal diseases (ie sacroiliac joint pain, anterior cruciate ligament-deficient, gluteal tendinopathy), also a different synergy structure compared to a control group was observed, but no difference in the number of muscle synergies.[17-19]

Recently, a new measure has been proposed called the Walking Dynamic Motor Control Index (Walk-DMC), which is based on the total EMG variance explained by one synergy.[15] The Walk-DMC has been proposed as a potential metric to assess the complexity of motor control and was shown to be associated with clinical outcomes after conservative treatment and orthopaedic surgery in patients with cerebral palsy.[15,20,21] Applying measures of complexity of neuromuscular control may also be a valuable clinical tool to assess the level of neuromuscular impairment in PWHA with different levels of joint damage.

The aims of this study are as follows: (a) to assess how haemophilic arthropathy affects the complexity of neuromuscular control during gait, (b) to investigate the relationship between complexity of neuromuscular control and joint impairment.

2 | MATERIAL AND METHODS

2.1 | Participants

This study was approved by the local ethical committee and conducted in agreement with the Declaration of Helsinki. All participants were informed about the purpose and procedures of the project and gave their written informed consent to participate in the study. Based on *non*-probability sampling, thirteen PWHA were recruited in two hospitals in Santiago (Chile), and thirteen healthy control subjects (student and employees) were recruited from the University of Chile (for their characteristics see Table 1).

Inclusion criteria for PWHA: Males, diagnosed with haemophilia A or B, severe or moderate (severe <1% and moderate 1%-5% of normal factor activity in blood), haemophilic arthropathy with a minimum of two points (sum knee and ankle in evaluated limb) of the Hemophilia Joint Health Score (HJHS), over 18 years of age and under 45 years, prophylaxis treatment with deficient factor (ie XIII or IX), and body mass index lower than 30. Exclusion criteria: History of hip, knee or ankle arthroplasty in the evaluated limb, equinus foot, incapacity to walking independently, history of muscle or joint bleeding in lower limbs in the last 2 months, chronic cardiac and/or respiratory pathology and neurological disease.

Inclusion criteria for control subject: Males over 18 years of age and under 45 years, no haemophilia and body mass index lower than

TABLE 1 Basic characteristics of the two groups

Variables	CG (n = 13)	PWHA (n = 13)	*P*-value
Age (years)	28.4 ± 6.2	28.7 ± 6.9	0.906
Body mass (kg)	75.5 ± 8.1	74.4 ± 8.7	0.280
Height (cm)	180 ± 0.04	170 ± 0.10	0.502
Body mass index	24.4 ± 1.9	25.3 ± 2.8	0.450
Pain during walk (VAS 0-10)	0 [0 0]	1 [0 6]	0.019*
Preferred velocity in 30 m (m/s)	1.2 ± 0.2	1.0 ± 0.2	0.016*
Physical activity (>150 min/wk)	7/13	4/13	0.223
PWHA were diagnosed with haemophilia A	NA	13/13	NA
Severity of haemophilia (severe)	NA	10/13	NA
Severity of haemophilia (moderate)	NA	3/13	NA
Evaluated limb			
HJHS ankle (points)	NA	7.1 ± 3.3	NA
HJHS knee (points)	NA	5.8 ± 4.9	NA
Sum HJHS knee and ankle (points)	NA	12.9 ± 6.0	NA
Contralateral limb			
HJHS ankle (points)	NA	5.2 ± 4.8	NA
HJHS knee (points)	NA	3.8 ± 5.0	NA
Sum HJHS knee and ankle (points)	NA	9.1 ± 8.9	NA

Parametric distribution: Mean ± SD. Nonparametric distribution: Median [Range]. CG, control group; HJHS, Hemophilia Joint Health Score; NA, Not applicable; PWHA, people with haemophilia; VAS, Visual Analogue Scale.
*P-value <0.05.

TABLE 2 Equations used for the muscle coordination analysis

Index	Equations
1. tVAF	$\left(\frac{\left[\sum_j^t \sum_i^m (\text{EMGr}-\text{EMGo})^2\right]}{\left[\sum_j^t \sum_i^m (\text{EMGo})^2\right]}\right)$
2. Walk-DMC	$100 + 10\left[\frac{\text{tVAFAVGc} - \text{tVAF1}}{\text{tVAFSDc}}\right]$

The total variance accounted for (tVAF). tVAF by one synergy (tVAF1). Original EMG data (EMGo). Reconstructed EMG data (EMGr). Dynamic motor control index (Walk-DMC). Average (AVGc) and standard deviation (SDc) of tVAF1 from the control group.

30. Exclusion criteria: Scoliosis, history of acute or chronic musculoskeletal disorders, cardiac and/or respiratory pathology and neurological disease.

2.2 | Data acquisition

In PWHA, the limb with the highest score on the HJHS was selected. In the control group (CG), the dominant limb was assessed, which was determined by asking the subjects which leg they would use to kick a ball.[22]

After shaving and cleaning the skin with alcohol, surface electrodes (Ag–AgCl, Kendall H124SG) were placed (interelectrode spacing 2 cm) on the following muscles according to SENIAM guidelines[23]: Medial Gastrocnemius (MG), Lateral Gastrocnemius (LG), Soleus (SOL), Tibialis Anterior (TA), Vastus Lateralis (VL), Medialis (VM), Rectus Femoris (RF), Semitendinosus (ST), Biceps Femoris (BF), Gluteus Maximus (GMAX) and Gluteus Medius (GMED).

Muscle activity patterns were assessed using a wireless EMG system (MyoSystem DTS; Noraxon USA Inc, Scottsdale, CA, USA), with a sampling rate of 1500 Hz. Gait cycle events were detected by a synchronized wireless pressure sensor placed underneath the heel of the foot.

2.3 | Experimental protocol

To assess if subjects had a sedentary lifestyle (<150 minutes per week of moderate physical activity), they were asked to indicate how many minutes per week they were involved in physical activity.[24]

Each subject was invited to walk barefoot overground at their preferred velocity and the CG also walked at a slower velocity similar to that of the mean preferred velocity in PWHA (1.0 m/s). Each

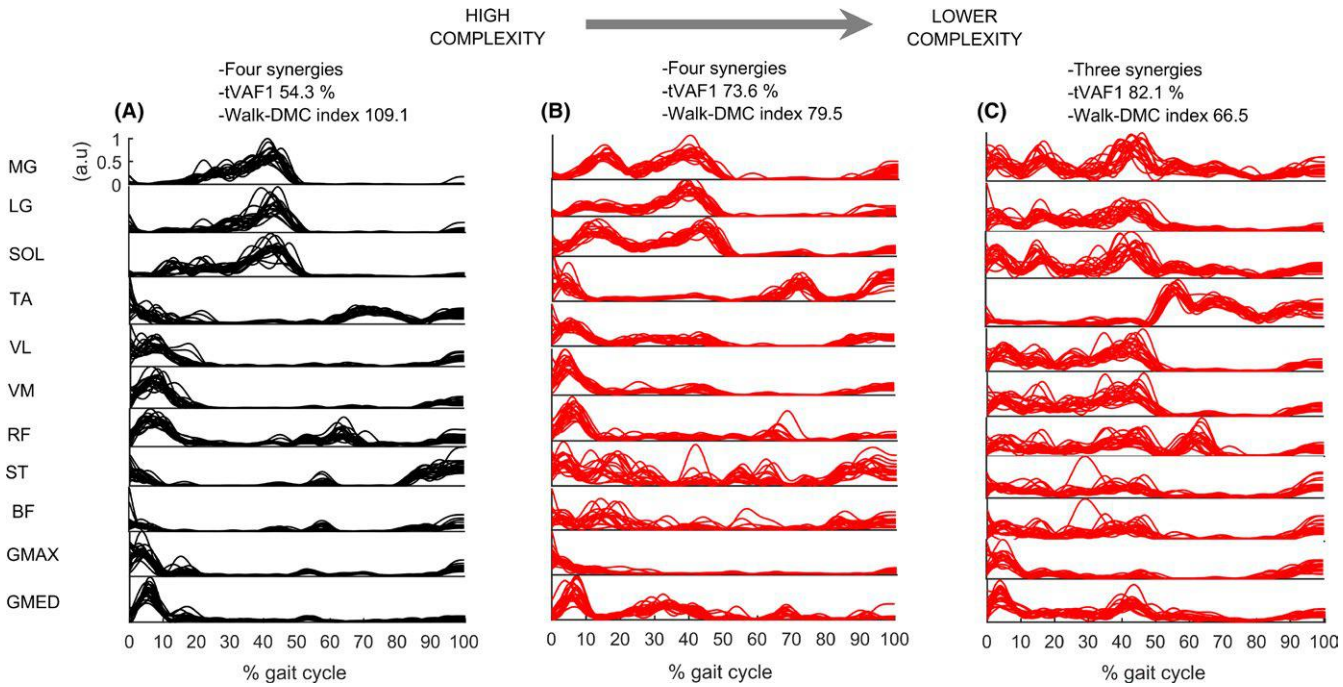

FIGURE 1 EMG activity patterns of multiple muscles during gait. A, Example of one healthy individual (black). EMG activity patterns during gait of two people with haemophilic arthropathy (PWHA) (red). B, Example of PWHA with low HJHS score in both knee and ankle (knee = 0 points; ankle = 2 points). C, Example of PWHA with high HJHS score in both knee and ankle (knee = 8 points; ankle = 8 points). The data show 20 gait cycles during slow velocity walking for the healthy subject (1.2 m/s) and the preferred velocity of the haemophilic patients (1.24 m/s and 1.03 m/s, respectively). Note that in PWHA, the EMG activity patterns of several muscles are similar indicating a high degree of co-activation between flexion and extension muscles. In the PWHA with high HJHS score (C), more than 80% of variance of all muscles can be explained by one synergy, while in the healthy subject one synergy explains only 54% of the variance. This can be explained by more co-activation between flexion and extension muscles and has been interpreted as an indication of more simplified control by the central nervous system. a.u., Arbitrary unit; BF, Biceps Femoris; GMAX, Gluteus Maximus; GMED, Gluteus Medius; LG, Lateral Gastrocnemius, MG, Medial Gastrocnemius; RF, Rectus Femoris; TA, Tibialis Anterior; SOL, Soleus; ST, Semitendinosus; VL, Vastus Lateralis; VM, Medialis. The total variance accounted for one synergy (tVAF1). The dynamic motor control index (Walk-DMC) [Colour figure can be viewed at wileyonlinelibrary.com]

velocity was practiced three times for 10 m. Mean velocity was assessed by dividing total distance by total time. Subsequently, each subject walked barefoot for 30-m, two times in each velocity, with 2 minutes of rest in between tests. Between 1 and 2 hours prior to the experiment, patients received prophylactic treatment.

2.4 | EMG data analysis

For the EMG and synergies analysis, Matlab software was used (MathWorks, Inc, Natick, MA, USA). For each condition in each group, 20 gait cycles were included for the analysis.

A bandpass filter (20-500 Hz) followed by rectification using Hilbert transformation was applied. Subsequently, EMG signals were low-pass filtered at 10 Hz and per condition normalized to the maximum value of all included cycles.[25,26] Then, EMG data was time normalized to 200 points.[25] Non-negative matrix factorization (NNMF) was used to extract muscle synergies from the EMG signals (for a comprehensive description see[27]). Briefly, the EMGs were combined into an $m \times t$ matrix, where m represents the number of muscles (11 in this study) and cycles (20 cycles), and t is the time base (200 points). The NMMF results in the muscle weightings (ie contribution) for each synergy (W) and the matrix encoding the activation pattern of each synergy (C). Note that the product of W and C should approximate the original EMG data.

The NNMF algorithm was iterated 20 times for each number of synergies between 1 and 4, and the iteration with the lowest reconstruction error was selected. The difference between reconstruction of EMG data and the original EMG data was calculated using the total variance accounted for (tVAF) (Table 2, Equation 1).[13] The tVAF was calculated for an increasing number of synergies (from 1 to 4). The number of synergies was increased until tVAF was >90% or until adding another synergy did increase tVAF by <5%.[13]

We used three measures to evaluate complexity of neuromuscular control:[15,28] (a) the number of synergies required for tVAF > 90%, (b) tVAF as a function of the number of muscle synergies and (c) Walk-DMC index. The Walk-DMC is a *z*-score based upon tVAF1, using the average and standard deviation of tVAF1 from the healthy CG (Table 2, Equation 2).[15] A higher tVAF1 results in a lower Walk-DMC score (see Figure 1).

2.5 | Clinical assessments for PWHA

To assess the intensity of pain (scale 0-10 points) during walking barefoot, the Visual Analogue Scale (VAS) was applied. The HJHS 2.1 score is used to assess joint health status in both knees and ankles.[29]

2.6 | Statistical analysis

For all statistical analysis, Matlab software was used (MathWorks, Inc). The alpha-level was set at 0.05. The normality of data were evaluated through the Shapiro-Wilk test. Data are expressed as the mean ± SD.

Two assessments were made for all variables: (a) the comparison of CG during preferred walking velocity (CG-pref) with PWHA, (b) and a comparison of CG during slow velocity (CG-slow) with PWHA.

The Chi-square test was used to compare the number of muscle synergies for tVAF > 90% between groups. To evaluate differences in the tVAF as a function of number of synergies, two-way repeated measures ANOVA (number of synergies × group) was used. Greenhouse-Geisser correction was used if the assumption of sphericity, as checked by Mauchly's test, was violated. If a significant interaction was found between factors, post hoc tests with Bonferroni correction were applied. To compare the Walk-DMC and muscle contributions of each synergy between groups, the independent samples *t* test was used. To determine the effect sizes of tVAF, Walk-DMC and muscle weightings the partial eta squared ($\eta_p^2 \geq 0.01$, $\eta_p^2 \geq 0.06$, $\eta_p^2 \geq 0.14$) and Cohen's ($d \geq 0.2$, $d \geq 0.5$, $d \geq 0.8$) were calculated, to indicate small, moderate or large effects, respectively.

Finally, to assess the relationship between complexity of neuromuscular control and joint impairment the HJHS score was correlated with the Walk-DMC index using Pearson correlation. In addition, *k*-means clustering analysis was applied to identify subgroups within the PWHA (ie different level of joint damage in the knee and/or ankle). The groups were considered distinct if the majority of silhouette values are larger than 0.6.[30] Subsequently, the Walk-DMC was compared between the identified subgroups of PWHA with the CG-slow using one-way ANOVA and post hoc with Bonferroni correction.

3 | RESULTS

3.1 | Anthropometric and clinical characteristics

Table 1 describes participant demographic and clinical characteristics. No difference was found ($P = 0.541$) in walking velocity of the slow condition in CG and preferred velocity in PWHA (1.0 ± 0.2 and 1.0 ± 0.2, respectively).

3.2 | Neuromuscular control

The number of muscle synergies for tVAF > 90% was not different between groups (ie median of four synergies, range 3-4 for CG-pref, 3-5 for CG-slow and 3-5 for PWHA), both when compared at preferred walking velocity ($P = 0.698$) and when compared at similar velocity ($P = 0.540$).

Comparing groups at their preferred velocity (Figure 2), two-way repeated measures ANOVA indicated a significant difference between groups ($P = 0.020$, $\eta_p^2 = 0.21$) and synergy number ($P < 0.001$, $\eta_p^2 = 0.94$), as well as a significant interaction ($P = 0.003$, $\eta_p^2 = 0.26$). Post hoc analysis showed a significant difference between groups only when including one synergy ($P = 0.003$, $d = 1.32$). When comparing groups for the similar walking velocity (Figure 2), two-way repeated measures ANOVA showed no significant difference between groups in tVAF as a function of the

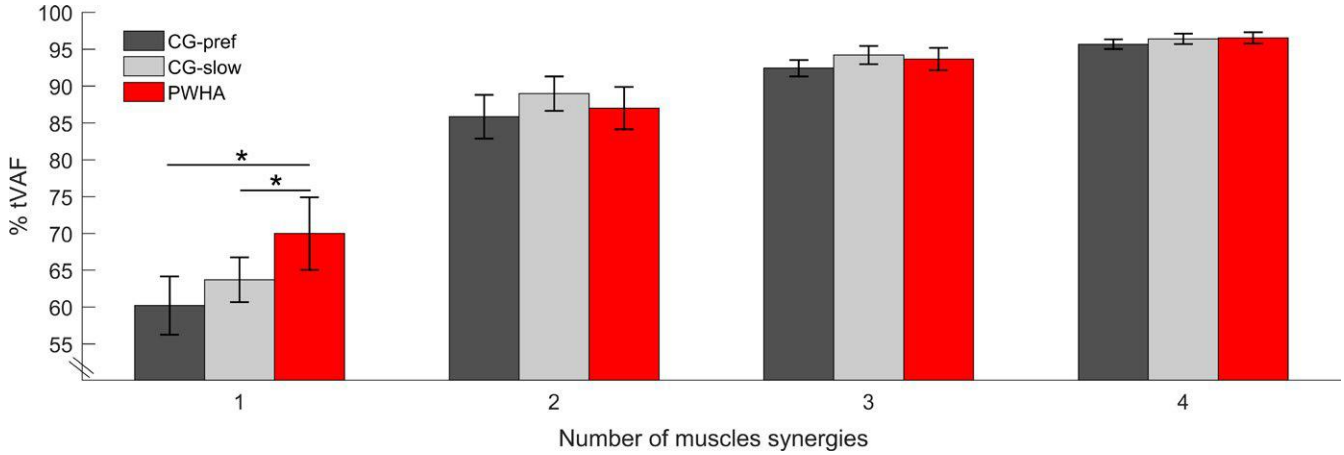

FIGURE 2 The total variance accounted for (tVAF) by one to four muscle synergies. A comparison between the control group (CG) during walking at the preferred (CG-pref) and at the slow (CG-slow) velocity and people with haemophilic arthropathy (PWHA) during walking at preferred velocity is shown. *$P < 0.05$ significant difference between CG and PWHA. Data are expressed as mean and 95% confidence intervals (n = 13 for both groups)

number of synergies ($P = 0.461$, $\eta_p^2 = 0.02$). A significant difference between synergy number ($P < 0.001$, $\eta_p^2 = 0.95$), and a significant interaction between group and synergy number was found ($P = 0.007$, $\eta_p^2 = 0.22$). Post hoc analysis showed a significant difference between groups only when including one synergy ($P = 0.027$, $d = 0.93$). These results indicate that in PWHA one muscle synergy can explain a greater part of the variance of the EMG data compared to the CG, independent of walking velocity.

For the Walk-DMC index, the PWHA showed a lower value compared with CG-preferred ($P = 0.003$, $d = 1.32$) and CG-slow ($P = 0.027$, $d = 0.92$) (Figure 3). For PWHA, no significant correlation was found between HJHS (sum knee and ankle) and Walk-DMC index ($r = -0.32$, $P = 0.28$).

Regarding muscle contributions of each synergy during gait at the same velocity (ie 1 m/s), a higher contribution was found for BF ($P = 0.008$, $d = 1.03$) and a lower for RF ($P = 0.023$, $d = 1.21$) in the acceptance synergy of PWHA (Figure 4). During the push-off synergy, a higher contribution of VL ($P = 0.040$, $d = 0.90$), RF ($P = 0.012$, $d = 1.10$) and ST ($P = 0.030$, $d = 0.81$) was found in PWHA (Figure 4). The consequence of these results is increased co-activation between antagonistic and synergistic muscles.

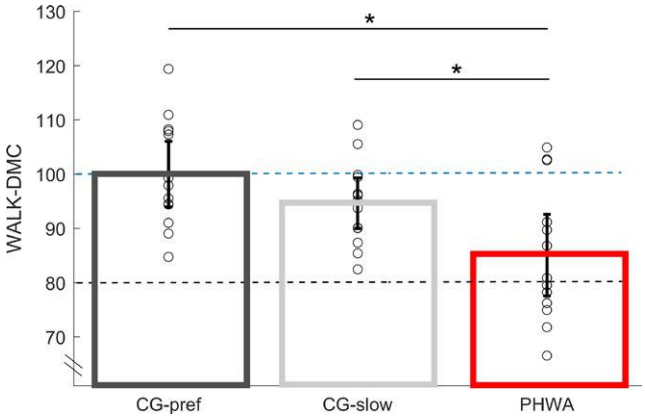

FIGURE 3 Dynamic Motor Control Index during Walking (Walk-DMC). A comparison between the control group during preferred (CG-pref) and slow walking velocity (CG-slow) and people with haemophilic arthropathy (PWHA) during preferred walking velocity. Blue horizontal dashed line indicates the normal value of Walk-DMC. Black horizontal dashed line indicates the 80 points of Walk-DMC, which is equal to two standard deviations (SD) from the normal value. *$P < 0.05$ significant difference between groups. The open circles indicate the individual data. Data are expressed as mean and 95% confidence intervals (n = 13 for both groups)

3.3 | Cluster analysis of HJHS of knee and ankle and Walk-DMC index

The *k*-means cluster analysis for the HJHS score resulted in two clusters. The silhouette value was 0.74 ± 0.12 for cluster 1 and 0.68 ± 0.06 points for cluster 2 (Figure 5A). Cluster 1 is characterized by a low HJHS score in the knee and cluster 2 by a high HJHS value in the knee (Figure 5B). The pain level and velocity during gait were similar between clusters ($P > 0.05$) (Table 3).

When compared at the similar velocity, one-way ANOVA revealed a significant group effect on Walk-DMC ($P = 0.019$, $\eta_p^2 = 0.29$). Post hoc analysis indicated a significant difference only between cluster 2 and the CG ($P = 0.016$, $d = 1.65$) (Figure 5C). No differences between clusters ($P = 0.245$, $d = 0.83$) and between cluster 1 and the CG ($P = 0.921$, $d = 0.41$) were observed.

4 | DISCUSSION

The main results of this study are as follows: (a) that on average the complexity of neuromuscular control (ie the extent of muscle co-activation) during gait in PWHA was different from healthy controls; and (b) that the complexity of neuromuscular control (Walk-DMC)

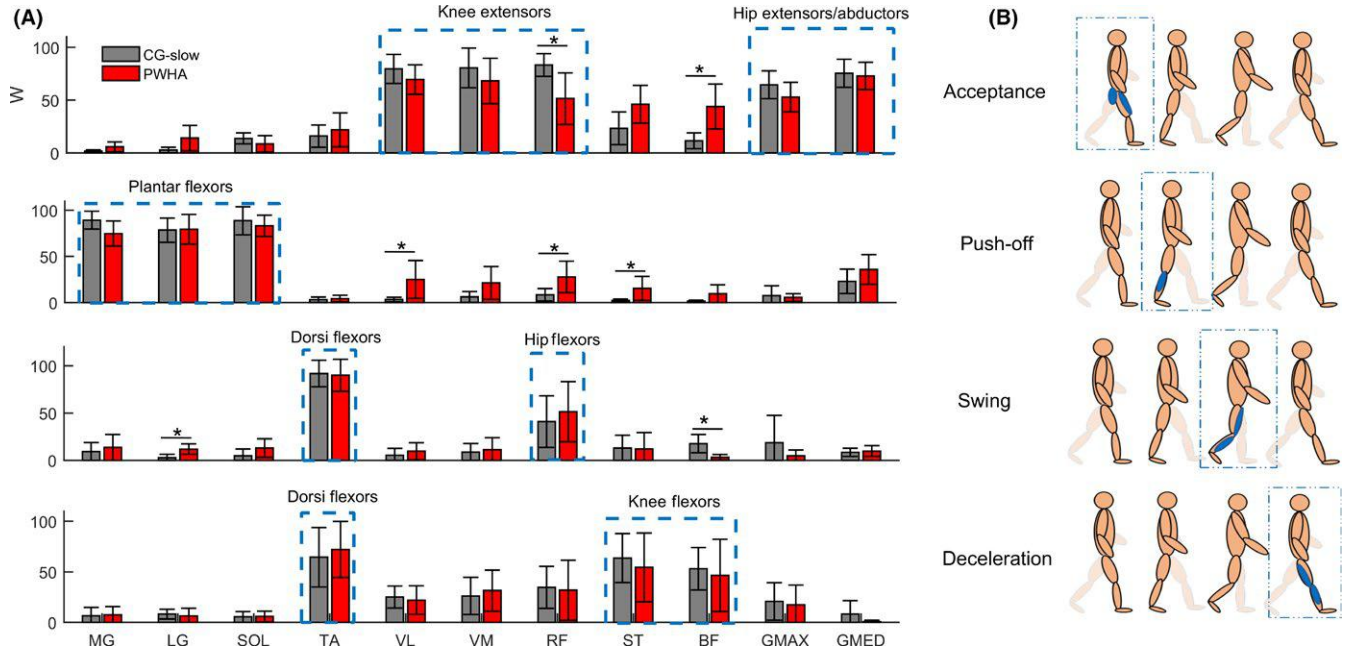

FIGURE 4 Comparisons of muscle contributions of each synergy during gait at the same velocity (ie 1 m/s). A, Comparisons of muscle contributions. Dashed blue line indicates the dominant muscle groups for each synergy. B, Schematic representation of the contribution of different muscles during gait. Dashed line and blue zone indicate the dominant muscle groups during each of the four phases. BF, Biceps Femoris; GMAX, Gluteus Maximus; GMED, Gluteus Medius; LG, Lateral Gastrocnemius; MG, Medial Gastrocnemius; RF, Rectus Femoris; SOL, Soleus; ST, Semitendinosus; TA, Tibialis Anterior; VL, Vastus Lateralis; VM, Medialis. Muscle weightings for each synergy (W). Slow walking velocity for the control group (CG-slow) and people with haemophilic arthropathy (PWHA) *P<0.05 significant difference between groups. Data are expressed as mean and 95% confidence intervals (n = 13 for both groups)

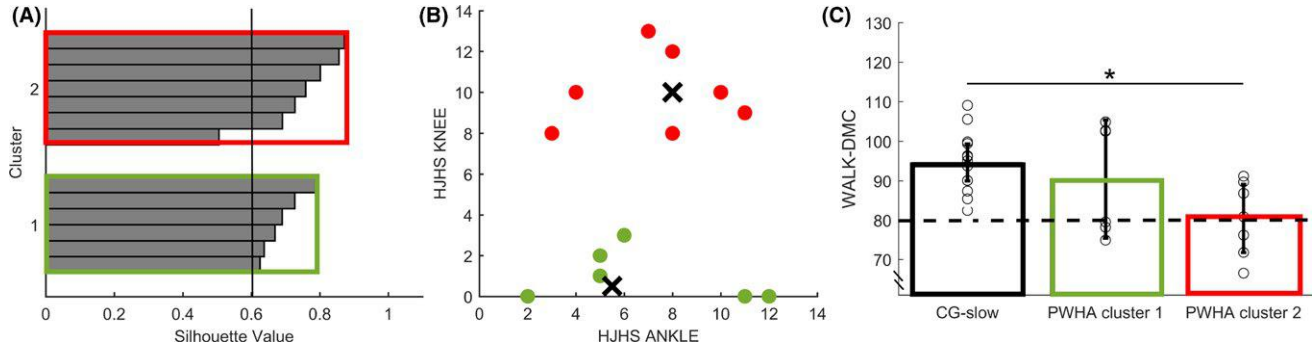

FIGURE 5 Relationship between joint impairment and Walk-DMC. A, The silhouette values. Note that the continuous line indicates the cut-off point (ie 0.6 value). B, Haemophilia Health Joint (HJHS) scores for knee and ankle of the limb evaluated with sEMG of all individuals for each cluster (green = 1, red = 2). Cluster 1 represents the people with haemophilic arthropathy (PWHA) with lower HJHS for the knee, while cluster 2 represents those PWHA with a high HJHS value for both knee and ankle. C, Comparison of the Dynamic Motor Control Index during Walking (Walk-DMC) at the same velocity (ie 1 m/s) between the control group during slow walking velocity (CG-slow, n=13), cluster 1 (n = 6) and cluster 2 (n = 7). Black horizontal dashed line indicates the 80 points of Walk-DMC, what is equal to two standard deviations (SD) from the normal value. *P < 0.05 significant difference between groups. Data are expressed as the mean and 95% confidence intervals. The circle indicates the individuals

was not correlated with ankle and knee joint health status (HJHS). To the authors' current knowledge, this study is the first to suggest an increased co-activation between synergistic and antagonistic muscles during gait in PWHA. This is clinically relevant, because a greater co-activation between antagonistic muscles could result in more intra-articular loading, resulting in greater progression of the osteoarthritis.[31]

The number of muscle synergies for tVAF > 90% in PHWA was not different than that in the CG. This is in agreement with previous reports on effects of musculoskeletal diseases.[17-19] In contrast, several studies have reported a lower number of muscle synergies in neurological diseases.[12,13] As the number of synergies is not a very distinctive measure, we also assessed other metrics of the complexity of neuromuscular control. We found significant

TABLE 3 Clinical characteristic between clusters in PWHA

Clinical variables	Cluster 1 (n = 6)	Cluster 2 (n = 7)	*P*-value
Evaluated limb			
HJHS ankle (points)	6.8 ± 3.8	7.3 ± 2.9	0.814
HJHS knee (points)	1.0 ± 1.2	10 ± 1.9	<0.001**
Sum HJHS knee and ankle (points)	7.8 ± 3.7	17.3 ± 3.7	<0.001**
Contralateral limb			
HJHS ankle (points)	3.7 ± 4.5	6.6 ± 5.0	0.300
HJHS knee (points)	1.2 ± 1.3	6.1 ± 6.0	0.077
Sum HJHS knee and ankle (points)	4.8 ± 4.2	12.7 ± 10.5	0.113
Pain and walking			
Pain during walking (VAS 0-10)	0 (0.5)	0 (0.6)	0.334
Preferred velocity in 30 m (m/s)	1.10 ± 0.19	0.99 ± 0.14	0.238
Physical activity (>150 min/wk)	1/6	3/7	0.308

Parametric distribution: Mean ± SD. Nonparametric distribution: Median [Range].
HJHS, Hemophilia Joint Health Score; VAS, Visual Analogue Scale.
**P-value <0.001 for comparison between clusters.

differences between PWHA and CG for tVAF1 and Walk-DMC. For tVAF1, the mean difference between PWHA and CG was more than 7%. This difference between groups is higher than inter-day measurement error of the tVAF1 reported for patients with cerebral palsy (ie 5%).[21] At the individual level, there was quite some overlap of Walk-DMC values between the two clusters for PWHA and CG. This suggests that some PWHA have normal neuromuscular control of gait.

The higher tVAF1 and lower Walk-DMC in PHWA can be explained by more co-activation of synergists and antagonists (see Figure 1). This is supported the increased co-activation of knee flexors and extensors during acceptance and push-off synergies (see Figure 4). Both results have been interpreted as indications of more simplified control by the CNS during gait.[13,15]

The z-score normalization of tVAF1 (ie Walk-DMC) has some advantages compared to the tVAF1. It is affected less by the different methods of EMG processing and it can be better compared across studies.[20]

The observed changes in neuromuscular control may be explained by different mechanisms. (a) Adaptations of the CNS to pain. Considering the temporal distinction between acute and chronic pain, different sources of pain, such intra-articular bleeding, inflammation of synovium and joint degeneration, as well alteration in pain perception in PWHA (eg altered central pain mechanisms)[32] may change the kinematics and kinetics of gait.[33] However, the pain levels during walking in the PWHA of the present study were rather low (see Table 1 and 2). Therefore, we do not expect pain to play an important role in our results. (b) The reduced range of ankle and knee joint motion. The chronic limitation of range of motion and disuse of the affected limb in PWHA may affect the mechanical properties of muscle and tendon .[2] Previous studies reported moderate-to-high correlations between muscle weakness and tVAF1 in patients with cerebral palsy and Duchenne muscular dystrophy .[34] In the present study, we did not find a significant correlation between the total HJHS score and Walk-DMC. However, this may be related to the limitations of the HJHS score. The HJHS involves a qualitative assessment with a small resolution (ie few levels), manual testing of force and testing range of motion during passive conditions only. We propose to include quantitative assessments of muscle strength and measurements of joint range of motion during gait in future studies. On the other hand, the subgroup of PWHA with an impairment of both knee and ankle joints showed a decrease in complexity of neuromuscular control (Walk-DMC) during gait compared to the subgroup with limitations in only the ankle joint. This indicates that neuromuscular control of gait is affected more in multi-joint impairment. (c) Disrupted proprioception. In PWHA, alterations in proprioceptive performance have been reported (ie angle-reproduction test).[2] (d) Impaired postural control. It has also been shown that static balance control is affected in PWHA.[35,36] The enhanced co-activation between flexors and extensors during gait, increasing joint stiffness, could be related to the reduced proprioception and impaired postural control.[37,38]

In the clinical context, the tVAF1 and Walk-DMC may be of additive value to assess the quality of neuromuscular control. Different approaches have been reported to enhance muscle function and joint range of motion, and reduce pain in PWHA.[39] However, in PWHA little is known about the impact of physical therapy on neuromuscular control. The selection of the best exercise protocol to reduce the extent of co-activation between joint flexor and extensor muscles could be relevant to prevent joint deterioration.[31,33,37] This

may help to improve solutions for rehabilitation after conservative treatment and orthopaedic surgery.[39,40]

A limitation of this study is that joint kinematics and kinetics were not assessed. Therefore, it is unclear if the gait movement pattern and mechanics were different in PWHA, and if this was related to the changes in neuromuscular control. In addition, a thorough analysis of the relationship between joint structure, muscle dysfunction and neuromuscular control is warranted, by adding radiological exams such as computed tomography, magnetic resonance imaging and sonography.

5 | CONCLUSION

The complexity of neuromuscular control during gait was reduced in PWHA by means of increased co-activation between synergistic and antagonistic muscles. Our results indicate that neuromuscular control is affected more in PWHA with multi-joint damage compared to single joint damage. The tVAF1 and Walk-DMC may be useful measures to assess changes in neuromuscular control in PWHA before and after rehabilitation therapies and or orthopaedic surgical interventions.

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DISCLOSURES

The authors state that they have no interests which might be perceived as posing a conflict or bias.

AUTHORS' CONTRIBUTION

CCM performed the research, designed the research study, contributed essential reagents or tools, analysed the data and wrote the paper. SPA and HM designed the research study, contributed essential reagents or tools, analysed the data and wrote the paper. MC analysed the data and wrote the paper.

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