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Author contributions

IRP initiated and coordinated the original study; all authors participated in the study design; AC, IRP and DJH analysed and interpreted results; AC and DJH wrote the manuscript; all authors revised and approved the final version of the manuscript.

Disclosures

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

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Joint damage and motor learning during unipedal stance in haemophilia arthropathy: report of two cases

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In haemophiliacs, repeated intraarticular bleeding causes major joint damage [1]. This damage affects proprioception, which is important for the appropriate control of a joint and to perform progressively difficult motor tasks [2].

To progress in therapeutic exercises, an adequate integration of sensory-motor inputs is necessary to correctly learn and execute motor tasks [2,3]. Conceptually, motor learning is related to practice or experience associated with processes that involve the acquisition or reacquisition of a skill, and this learning can be evaluated through the number of errors or successful/failed attempts made during task execution [4].

There has been some interest within the last decade in using postural balance to assess the sensorimotor system in adult patients with haemophilic arthropathy, who show impaired postural control compared to healthy subjects [5]. Despite this knowledge, the sensorimotor integration process and assessments of motor learning during balance exercises associated with joint damage in haemophilia patients are poorly understood and scarcely used in rehabilitation programs.

The unipedal stance is a common task used to improve sensorimotor integration, stability and joint protection. This stance requires different motor synergy configurations of the lower limbs and trunk [6], as well as inherent feedbacks from mechanoreceptor

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Table 1. Radiological and clinical assessments.

	Hip		Knee		Ankle	
	Subject A	Subject B	Subject A	Subject B	Subject A	Subject B
Pettersson	0	7	10	10	0	9
Gilbert	NT	NT	7	9	0	4

Radiological evaluation or Pettersson Score, with a maximum of 13 points; Physical Examination Score or Gilbert Score, with a maximum of 12 points. NT, Non-testable.

afferents from the skin, muscle spindle, Golgi tendon organ and joint capsule [2,4]. Augmented feedback, understood as sensory information additional to inherent feedback, is a common strategy used to reduce task errors and is based on auditory, tactile or visual reinforcement stimuli [4].

In haemophiliacs, alterations in sensorimotor integration as a result of joint damage could affect both motor performance and motor learning. As a result, these patients are at a potential disadvantage for making progress in therapeutic balance exercises, consequently leading to an increased risk for intraarticular bleeding. This is the principal difference with other chronic joint damage, such as osteoarthritis.

The aim of this case study was to use augmented visual-stimulus feedback to describe the sensorimotor learning process over three consecutive days in two haemophiliacs with different degrees of joint damage while performing a unipedal balance task.

With the prior approval of the local ethics committee, two subjects were recruited. To describe motor learning during unipedal stance, the exclusion criteria were adult patients with intraarticular bleeding within the last 12 months and no pain perception during the unipedal task. The inclusion criteria were adults between 35 and 45 years old, a body mass index (BMI) between 20 and 30 kg m^{-2}, similar quantity of previous training sessions on unipedal stability, similar educational levels, and different levels of joint damage in the lower limbs.

Subject A had moderate haemophilia with arthropathy only in the knee of the dominant limb, and subject B had severe haemophilia and joint damage in the hip-knee-ankle of both limbs. Subject A was 44 years-old and had a BMI of 27.7 kg m^{-2}. Subject B was 38 years-old and had a BMI of 23.5 kg m^{-2}. All of the considered clinical variables are shown in Table 1.

A program was designed in the Matlab® 2015 software (Mathworks Inc., Natick, MA, USA) to deliver real-time visual feedback through the inertial sensor of an iPhone 6 Smartphone (Apple Inc, Cupertino, USA) fixed at the level of the sternum. When fixed in this location, iPhone sensors provide sufficient validity and intraday reliability for kinematic evaluations during dynamic balance tests [7]. The data were transferred using the Matlab Mobile™ application (Matlab Support Package for Apple iOS Sensors), with a sampling

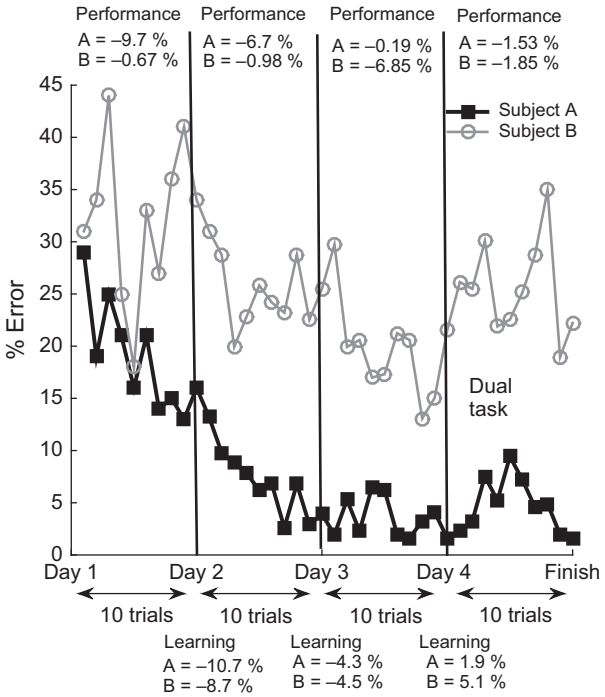

Fig. 1. Motor learning curve. Differences in performance error rates for unipedal balance trials (days 1-3) and for dual task trials (day 4).

rate of 10 Hz. Following calibrations of the iPhone sensor, accelerations were recorded in the axes (X, Y and Z). Jerk analysis was used, which is defined as the acceleration change rate and is calculated by deriving acceleration relative to time [8].

To establish an exercise threshold, the maximum jerk generated without visual feedback was first evaluated in a 30-s test. This amount of time was established to prevent patient pain while also gathering enough data. For both analysis and feedback, the sum of the jerk in all three axes was used. In both subjects, 35% of the highest jerk generated by an initial test was selected to choose the exercise threshold. Any value greater than the threshold was considered an error, and the error ratio was determined as the percentage of all recorded values over the threshold.

Each subject was asked to perform ten consecutive trials of the unipedal balance task using the dominant limb, with 1 min rests between tests and an emphasis on avoiding pain and fatigue during the test. The performance curve was assessed on three consecutive days. Subsequently, to evaluate learning consolidation, the same task was measured on a fourth day, but was combined with a cognitive dual task of counting backwards from one hundred in threes. Adding a dual task allows exploring the extent to which subjects have progressed towards the automatic stage of motor-sensory learning [4]. Performance ratings of each session were defined as the percent difference in the error ratio between the mean of the first three and last three

trials. This analysis is more representative of task performance than a single value. In turn, motor learning was determined by the percent difference of errors across all trials between days [4].

The study outcome showed that both subjects had the same percentage of errors in the first trial. However, performances between the first, second, and third days were different between subjects (Fig. 1). Subject A presented a decreased percentage of error on the first and second days and stabilized performance on the third. Meanwhile, subject B only achieved better performance on the third day (Fig. 1). During the dual task, the error of subject A increased by 1.9%, whereas the error of subject B increased by 5.1%. Incorporating a dual task during the evaluation of postural control is commonly used as a way to isolate the automatic control component from the cognitive component [9]. The differences between the two subjects reflect the degree of automaticity after 3 days, suggesting there may be differences in motor learning process between subjects, possibly due to changes in sensorimotor integration associated with differences in joint damage.

The generated learning curve showed that while both subjects improved their performance throughout the course of the trial, each subject presented different error rates. Subject A not only achieved better increases in performance from day one, but was also able to improve consolidated motor learning once subjected to a dual task. These results suggest that both joint damage and the number of damaged joints may influence proper task execution. This would affect performance and could be related to different processes in motor learning, with a marked difference in performance during the first days. However, it is important to mention that the motor learning curve for one specific task can be affected by other factors, including attention, motivation, sleep quality, and previous experience [4].

To our knowledge, this is the first report to suggest that haemophilic arthropathy may affect performance during a sensorimotor stability task and subsequent learning. Moreover, this study used the inertial sensor built into a smartphone, a technology already used to improve balance through vibrotactile feedback [10]. Therefore, visual feedback based on jerk analysis could be incorporated to gradually change the complexity of the different types of balance exercises and to record the motor learning curve of new tasks.

To generate a learning curve, the augmented feedback threshold must be verified as sufficient for producing more than habitual cognitive and motor demands [4]. In this case report, a threshold of 35% of the maximum jerk was used for both subjects; however, future studies are needed to more accurately establish the optimal threshold. Moreover, it is important to consider that while the visual feedback used in this report was the jerk value, there are other variables or indicators, such as angular velocity, acceleration or tilt, that could be evaluated in future studies.

One advantage of the present methodology is that this technology can be used for both assessing and treating the sensorimotor system, information that can be subsequently applied to design patient-individualized rehabilitation balance programs. Within the limitations and disadvantages of this study, it is important mention the final results and interpretations could be affected by correct choices for threshold work, the days necessary for evaluating the motor learning curve, and repeatability of device placement between test days. Furthermore, this study represents a first approach to assessing interactions between joint damage and motor learning in haemophilic patients, and future studies are needed that consider a greater sample size and that perform comparisons with healthy control subjects to corroborate the real impact of haemophilic arthropathy on motor learning.

Finally, it is worth mentioning that, from a clinical point-of-view, the motor learning curve may be useful for designing rehabilitation programs that facilitate progress to more complex tasks. In addition, the learning curve could complement clinical examines, which might result in better clinical outcomes, thus favouring the future prophylaxis of patients with haemophilic arthropathy. This report provides a foundation for new lines of deeper research into aspects associated with haemophilic arthropathy and motor performance during balance exercises.

Author contributions

CC, GR and FQ participated in research design. CC, GR, JT and PB performed the intervention and data collection. CC, GR, JT, PB and SP analysed the data. CC wrote the paper, and all authors critically reviewed the final version of the paper.

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

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Epidemiology of bleeding symptoms and hypermobile Ehlers-Danlos syndrome in paediatrics

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Ehlers-Danlos syndrome (EDS) is characterized by tissue fragility, skin hyperextensibility and joint hypermobility [1]. Hypermobile EDS (hEDS) is generally accepted to be the most common subtype. Bleeding and bruising are common findings in patients with all EDS subtypes, affecting >90% of patients in one large cohort [2]. However, a systematic assessment of bleeding severity and frequency in hEDS has not been previously reported. Thus, in this study we sought to (i) quantify bleeding severity in children with hEDS using a validated bleeding assessment tool (BAT) [3] and (ii) screen children referred for bleeding symptom evaluation for hEDS, to assess the prevalence of hEDS within a paediatric haemostasis clinic referral population [1]. Better understanding this epidemiology may further the investigation of appropriate management of hEDS-related bleeding. In addition, improved recognition of hEDS in patients referred for bleeding symptoms may facilitate proper diagnosis and institution of appropriate hEDS-related health surveillance for musculoskeletal disease, autonomic dysfunction and other functional disorders.

Following Nationwide Children's Hospital Institutional Review Board (IRB11-0110) approval, patients were recruited through either an outpatient Genetics or Haemostasis visit between July 2011 and February 2013. Beighton scores are known to demonstrate non-specific increased mobility in children <9 years old, making it difficult to distinguish pathologic from polymorphic hypermobility [1,4]. Thus, children aged 9–21 years were eligible for participation and were approached, prospectively, as they presented to each clinic. Patients with pre-existing haemostasis diagnoses or another hereditary disorder of connective tissue (HDCT; e.g. Marfan or Loeys-Dietz syndrome) were excluded.

The Paediatric Bleeding Questionnaire (PBQ), based upon a BAT designed for adult patient evaluation, has been validated to screen children for vWD [3,5]. Originally designed for children <18 years old, the PBQ has subsequently demonstrated specificity for adult vWD [6]. The PBQ is suspicious for vWD when ≥2. Although the PBQ has not previously been applied to hEDS it provides a method to objectively quantify bleeding in paediatric settings.

New patients presenting to Genetics clinic and meeting Villefranche criteria for hEDS diagnosis were eligible for recruitment [1]. The major diagnostic criteria for hEDS are (i) generalized joint hypermobility (Beighton ≥ 5), which is necessary for the clinical diagnosis, and (ii) skin hyperextensibility and/or smooth, velvety skin. Minor, diagnostic criteria for hEDS are recurring joint dislocations, chronic joint/limb pain, and positive family history. Patients were evaluated by one of two dysmorphologists using the Villefranche criteria and objectively assigned a Beighton score by a physical therapist using a goniometer [7]. Three physical therapists (PT) were

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