Gait & Posture 82 (2020) 54–60

Contents lists available at ScienceDirect

Gait & Posture

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

Full length article

Botulinum toxin injections minimally affect modelled muscle forces during gait in children with cerebral palsy

M. Wesseling [a], H. Kainz [a,c], T. Hoekstra [a], S. Van Rossom [a], K. Desloovere [b], F. De Groote [a], I. Jonkers [a,*]

[a] Human Movement Biomechanics Research Group, Department of Movement Sciences, KU Leuven, Leuven, Belgium
[b] Research Group for Neurorehabilitation, Department of Rehabilitation Sciences, KU, Leuven, Belgium
[c] Department of Biomechanics, Kinesiology and Computer Science in Sport, Centre for Sport Science and University Sports, University of Vienna, Vienna, Austria

ARTICLE INFO

Keywords:
Cerebral palsy
Musculoskeletal modelling
EMG-constrained optimization
Botulinum toxin type A injections

ABSTRACT

Background: Children with cerebral palsy (CP) present altered gait patterns and electromyography (EMG) activity compared to typically developing children. To temporarily reduce muscular activity and to correct the abnormal muscle force balance, Botulinum Toxin type A (BTX-A) injections are used.
Research question: What is the effect of BTX-A injections on dynamic muscle forces during gait, when calculated using an EMG-constrained approach?.
Methods: Retrospective data of ten typically developing (TD) and fourteen children with spastic diplegic CP were used for musculoskeletal modeling and dynamic simulations of gait, before and after BTX-A treatment. Individual muscle forces were calculated using an EMG-constrained optimization, in which EMG of eight muscles was used as muscle excitation signal to constrain the muscle activation patterns. Paired t-tests were used to compare average modelled muscle forces in different phases of the gait cycle pre- and post-BTX-A, summarized in the muscle profile score. Two-sample t-tests were used to determine significant differences between TD and pre- and post-BTX-A modelled muscle forces.
Results: For most muscles, the force was decreased in CP compared to TD children in all phases of the gait cycle, both before and after BTX-A treatment. Differences in muscle forces before and after BTX-A treatment were limited, with only few significant differences between pre- and post-BTX-A. Compared to a standard static optimization approach, imposing the EMG activity increased modelled muscle forces for most muscles.
Significance: Our findings indicate that BTX-A treatment has a limited effect on the muscle balance in CP children. Besides that, the use of EMG-constrained optimization is recommended when studying muscle balance in children with CP.

1. Introduction

Children with cerebral palsy (CP) have altered electromyography (EMG) activity and gait patterns compared to typically developing children (TD) [1]. Reduced voluntary activation [2], as well as inappropriate timing and increased co-activation of antagonist muscles were reported based on EMG measurements [1]. Although EMG is directly linked to muscle action and reflects the excitation state of the muscle, it is not proportional to muscle force during dynamic contractions (e.g. during gait), because the muscle length and muscle contraction velocity affect its relation to muscle force [3].

Botulinum Toxin type A (BTX-A) injections are used to correct the abnormal muscle balance in children with CP [4]. BTX-A temporarily reduces muscular activation following injections [4,5]. When used in treating abnormal muscle tone and spasticity, it provides a period of tone reduction of about 12–16 weeks [5]. During this period, improvement in functional ability can be achieved when combined with intensive physiotherapy, casting and orthotic management [5,6]. Treatment with BTX-A injections were found to improve spatiotemporal parameters, ankle dorsiflexion and knee extension angles, as well as hip range of

* Corresponding author at: Tervuursevest 101 – box 1501, 3001, Leuven, Belgium.
E-mail addresses: mariska.wesseling@kuleuven.be (M. Wesseling), hans.kainz@univie.ac.at (H. Kainz), tessa.hoekstra@kuleuven.be (T. Hoekstra), sam.vanrossom@kuleuven.be (S. Van Rossom), kaat.desloovere@uzleuven.be (K. Desloovere), friedl.degroote@kuleuven.be (F. De Groote), ilse.jonkers@kuleuven.be (I. Jonkers).

https://doi.org/10.1016/j.gaitpost.2020.08.122
Received 31 May 2019; Received in revised form 10 July 2020; Accepted 18 August 2020
Available online 22 August 2020

Table 1
Subject characteristics with mean (standard deviation) and MRC and Ashworth scales with median [range].

		CP-pre	CP-post	TD
Age		7.27 (1.16)	7.54 (1.12)	8.00 (1.60)
Weight		22.59 (4.46)	23.19 (4.85)	28.70 (6.19)
Lenght		1.21 (0.08)	1.24 (0.09)	1.32 (0.11)
BMI		15.32 (1.63)	15.05 (1.62)	16.23 (1.58)
Gender		9M/5F	9M/5F	6M/4F
Walking speed		0.95 (0.25)*	0.90 (0.20) *	1.19 (0.15)
Normalized Walking speed		0.41 (0.11)	0.40 (0.11) *	0.49 (0.075)
GMFCS level		I:4 II:10	–	–
Time GA after treatment		–	58.43 (12.21)	–
MRC	**Hip flexors**	4 [3,5]**	4 [3,4]**	–
	Hip extensors	4 [3,5]	4 [2,5]	–
	Hip abductors	3 [3,4]	3 [2,4]	–
	Hip adductors	4 [3,5]	4 [3,5]	–
	Knee flexors	3 [3,5]	3 [3,4]	–
	Knee extensors	4 [3,5]	4 [3,5]	–
	Ankle dorsiflexors, knee 90°	3 [2,4]	3 [1,4]	–
	Ankle dorsiflexors, knee 0°	3 [2,4]	3 [1,4]	–
	Ankle plantarflexors	3 [1,5]	3 [1,4]	–
	Hip flexors	1 [0,2]**	0 [0,2]**	–
	Hip adductors (knee 0° flexion)	1.5 [0,2] **	1 [0,2]**	–
	Hip adductors (knee 90° flexion)	1 [0,1.5] **	0 [0,1.5]**	–
Ashworth	**Hamstrings**	1.5 [0,3]	1.5 [0,3]	–
	Duncan elly	0 [0,1.5]	1 [0,2]	–
	Soleus	1.5 [0,3]	1.5 [1,2]	–
	Gastrocnemius	2 [1.5 3]**	2 [1.5,3]**	–
	Tibialis posterior	0 [0,2]	0 [0,2]	–
	Clonus	1 [0,2]	0 [0,3]	–

* Indicates a significant difference from the TD children.
** Indicates a significant difference between CP patients pre- and post-BTX-A treatment.

motion [7–10]. In addition, increased muscle length and normalized ankle kinetics after BTX-A treatment were found [10,11]. Interestingly, BTX-A injections did not improve surface EMG patterns during gait in children with CP although their functional ability improved [12]. However, only a few muscles can be measured with surface EMG. Besides that, the effect of BTX-A injections on the dynamic muscle force distribution during gait has not been studied.

A better understanding of dynamic muscle forces can be gained through musculoskeletal modeling. Modeling already provided valuable insights in the mechanisms behind crouch gait and muscle weakness in CP [13,14]. As the musculoskeletal system is redundant, optimization techniques are used to determine the muscle force distribution. Typically, minimization of muscle activations is the most common optimization criterion [15–17]. However, this optimization criterion is not appropriate for use in CP children, as it calculates minimal co-contraction, whereas measured EMG signals show an increased co-contraction in these children [1]. Therefore, EMG signals should be taken into account when calculating muscle forces. Previous research indeed showed that an EMG-constrained optimization method tracks experimental joint moments and EMG-excitations well in healthy subjects and in children with CP.

The aim of this study was to investigate the effect of BTX-A injections on dynamically modelled muscle force distribution during gait. Muscle forces were calculated using an EMG-constrained approach to account for the pathological neuromuscular control strategy of each child with CP. Based on previous research, which showed functional improvements after BTX-A injections [5,6], we hypothesized that BTX-A injections would decrease forces of spastic muscles during walking and therefore lead to a closer to typically developing muscle force distribution pattern.

2. Methods

2.1. Participants

Fourteen children with spastic diplegic CP who underwent BTX-A treatment between 2009 and 2015, were selected from the database of Clinical Motion Analysis Laboratory of the University Hospitals Leuven. A homogeneous group of children that received a similar approach of multilevel treatment with BTX-A injections, predominantly in the gastrocnemius, hamstrings and psoas muscles, was selected (supplementary material table S1). Children were included if they were able to walk independently for at least 10 m and had a GMFCS (Gross Motor Function Classification System) score of I or II. Children who underwent previous orthopedic surgery or more than four previous BTX-A treatments were excluded. Additionally, the data of ten typically developing (TD) children were included from the database. Participant characteristics are shown in Table 1. The dosage of BTX-A injection (Botox®) is reported in supplementary material (Table S1). Medical Research Council (MRC) strength and Ashworth spasticity scores were measured in the CP patients before and after BTX-A. Due to lack of patient compliance, the MRC score could not be measured in some patients for the hip extensors (2 patients), hip abductors (1 patient), hip adductors (1 patient), ankle dorsiflexors (1 patient) and ankle plantarflexors (3 patients). The Ashworth score of the tibialis posterior could not be measured for one patient. All participants and/or their legal guardians signed informed consent. Approval to access the retrospective database was obtained from the local Ethical Committee (S57746).

2.2. Motion capture

Three-dimensional motion capture data of all children with CP were collected before and after BTX-A treatment. The TD children underwent a single 3D gait analysis. During the gait analysis, participants walked barefooted on a 10 m walkway at a comfortable, self-selected speed without the use of walking aids. Reflective markers were placed on bony landmarks following the lower body Vicon plug-in-gait model [18] and marker trajectories were measured using a Vicon motion capture system (Oxford Metrics, Oxford, UK; 100 or 120 Hz, dependent on the lab configuration history). Ground reaction forces were measured using two AMTI force plates (Advanced Mechanical Technology Inc., Watertown, MA, USA; 1000, 1500 or 1560 Hz, dependent on the lab configuration history). Surface EMG was measured (Zerowire system, Cometa, Milan, IT; 1000, 1500 or 1560 Hz, dependent on the lab configuration history) for the gluteus medius (middle part), vastus lateralis, rectus femoris, biceps femoris (long head), semitendinosus, tibialis anterior, soleus, and gastrocnemius muscles. Due to measurement issues (such as artefacts or technical problems), in some participants EMG signals of the gluteus medius (in 3 pre- and 2 post-BTX-A participants), semitendinosus (in 2 pre- and 1 post-BTX-A participants), vastus lateralis (in 1 TD and 1 pre-BTX-A participants) and rectus femoris (in 1 TD and 1 post-BTX-A participants) were missing. EMG was band-pass filtered between 20−400 Hz, rectified, low-pass filtered at 10 Hz and normalized to the maximum value within the gait trial. For each participant, at least three representative left and right strides were selected.

2.3. Musculoskeletal modeling

OpenSim 3.3 [16] was used to calculate the muscle forces during gait. A modified version of the generic gait2392 OpenSim model was used as a reference model. This model included three rotational degrees of freedom (DOF) at the hip and knee joint, one rotational DOF at the ankle joint, 92 muscle-tendon actuators and a coordinate limit force to

simulate passive forces in knee hyperextension. The model was scaled to the anthropometry of each participant using the 3D marker positions from the static trial and the participant's body mass [19]. Additionally, maximal isometric muscle forces in the model were scaled to body mass to the power of 2/3 [15]. Joint angles were calculated using a Kalman smoother procedure [20] and joint moments were calculated with the standard inverse dynamics tool in OpenSim [16]. Individual modelled muscle forces during gait were calculated with only one DOF (flexion/extension) in the knee using an EMG-constrained approach.

2.3.1. EMG-constrained approach

To account for the individual motor control of each child, an EMG-constrained approach was used to calculate muscle forces during walking. In the EMG-constrained approach (implemented in Matlab 2015b), the processed EMG signal was used to constrain the calculated muscle activation patterns, taking into account an electromechanical delay of 0.05 s upon the EMG signals [21]. As the EMG signals could not be scaled to the maximal activation, an individual scale factor of each EMG signal was minimized within the cost function:

$$min_{a,s_{EMG}} = \sum_{m,s_{EMG}}^{43} \left(a_m(t_i) + s_{EMG}\right)^2 + \sum_{dof}^{5} M_{ID} + M_m,$$

subject to $a_m * s_{EMG} - 0.1 * \ a_{m-SO} \leq \ a_m \leq \ a_m * s_{EMG} + 0.1 * \ a_{m-SO}$,

where a_m is the muscle activations, t_i is the time frame, s_{EMG} the scale factors for the EMG signals, M_{ID} the inverse dynamics joint moments and M_m the muscle joint moments. The constrained muscle activations were allowed to deviate from the scaled EMG signal by maximally 10 % of the maximal activation calculated using a standard static optimization (SO) approach ($a_{m\text{-}SO}$). Muscles for which no EMG signals were available were free to vary at each time step. The EMG signals were scaled within the EMG-constrained optimization, as the magnitude of the EMG activities relative to the maximum activations were not known. Due to muscle weakness and impaired muscle coordination, the measurement of maximum voluntary contractions in children with CP is unreliable [2] and therefore a normalisation of EMG to a maximum activation was not possible. The gastrocnemius EMG signal was imposed to both the lateral and medial head of the muscle, due to a lack in consistency of the retrospective EMG data. While in the children with CP the lateral gastrocnemius was measured, in most of the TD children the medial gastrocnemius was measured. However, medial and lateral gastrocnemius can be expected to present similar EMG activity [22]. To investigate if the results observed using an EMG-constrained approach would change compared to when using a standard SO approach that does not account for the measured EMG signals, we compared both approaches. This analysis can be found in supplementary material.

2.4. Data analysis

Similar to the gait profile score [23] and gait kinetic index [24], root-mean-square-differences between the CP and TD participants for the joint angles and moments in all degrees of freedom in the model were compared pre- and post-BTX-A treatment. Modelled muscle forces were compared between the pre- and post-BTX-A gait assessment and between CP and TD participants, for which the gait cycle was divided in four phases (initial double support (IDS), single stance (SS), terminal double support (TDS) and swing (SW)) based on the events of initial contacts and toe offs. For each phase, the average modelled muscle forces were calculated and normalized to body mass. For each participant, all variables were averaged over the available trials for the left and right leg separately and analyzed as independent samples. In addition, the Individual-Muscle-Score and Muscle-Profile-Score (MPS) were calculated and illustrated in the Muscle-Force-Profile (MFP) [28]. The MPS was calculated as the mean of the root-mean-square differences between the CP and average TD modelled muscle force waveforms over all analyzed individual muscles. The Individual-Muscle-Score was determined as the root-mean-square difference between the CP child's modelled muscle force waveform and the average waveform of the TD children.

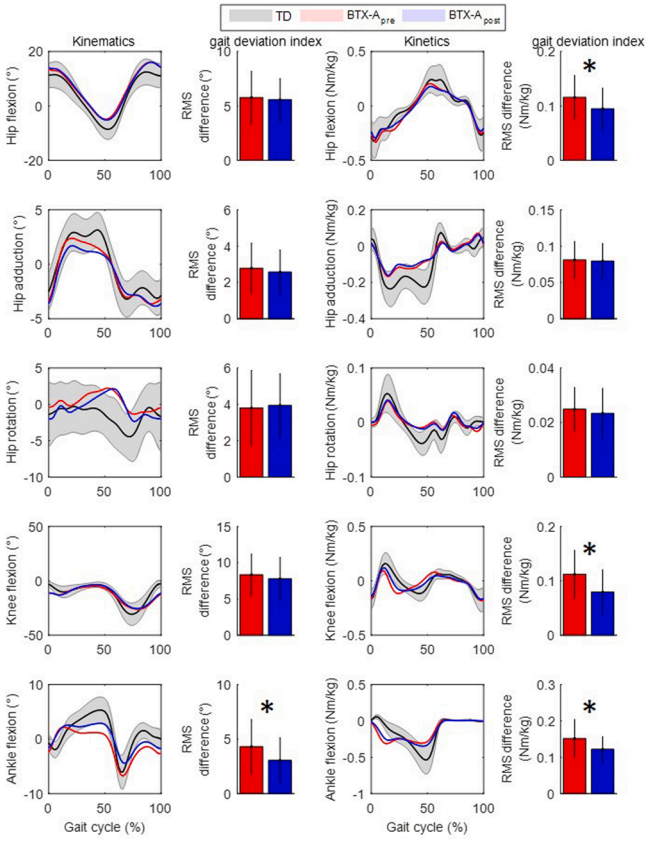

Fig. 1. Kinematic and kinetic waveforms with the root-mean-square (RMS) difference for each degree of freedom. Asterisks (*) indicate significant differences in RMS differences before and after BTX-A treatment.

To determine statistical differences in age, weight, height, body mass index (BMI), gait speed and normalized gait speed between the TD and CP children, two-sample independent t-tests were used. Gait speed was normalized to leg length following [25]:

$$v_{norm} = v / g * ll^{2/3}$$

Where v_{norm} is the normalized walking speed, v is walking speed, g is gravitational constant (9.81 m/s^2) and ll is the leg length calculated as the 3D distance from the hip joint center to the ankle joint center. MRC strength and Ashworth spasticity scores were compared before and after BTX-A treatment using a Wilcoxon signed rank test.

To evaluate the effect of BTX-A treatment, a paired *t*-test was used to compare modelled muscle forces before and after BTX-A treatment. A two-sample *t*-test was used to determine significant differences between TD and pre-BTX-A and TD and post-BTX-A modelled muscle forces. In addition, the MPS for the injected and non-injected muscles were compared using a paired *t*-test. Significance level was set at $\alpha = 0.05$ (2-tailed).

3. Results

The weight and height of the TD children was significantly higher compared to the CP children both pre- and post-BTX-A treatment, while BMI was not significantly different. Gait speed was significantly faster in TD compared CP children before and after treatment. Normalized gait speed was only significantly slower in CP children post-BTX-A treatment

Table 2
Average muscle force for TD children and CP children before and after BTX-A treatment calculated using EMG-constrained (N/kg) generated for all muscles in the model where the force was more than 1.5 N/kg. Results of the statistical analysis comparing the CP patients pre and post-BTX-A treatment (paired *t*-test), pre- and post-BTX-A with TD (two-sample *t*-test) are presented. Muscles printed in italic were injected with BTX-A, muscles with an asterisk were measured using EMG. Underlined p-values show a difference in significant results depending on the use of static optimization (see supplementary material) or EMG-constrained. Significant p-values are printed in bold.

		Muscle force EMGcon (N/kg)			p-value using EMGcon		
		TD	BTX-A_{pre}	BTX-A_{post}	TD vs BTX-A_{pre}	TD vs BTX-A_{post}	BTX-A_{pre} vs BTX-A_{post}
IDS	Glut med ant	1.98	1.10	1.00	**0.02**	**0.00**	0.52
	Glut med mid*	1.69	0.95	1.01	**0.01**	**0.02**	0.68
	Glut med post	1.94	1.72	1.76	0.62	0.69	0.83
	Semimembranosis	5.52	3.96	3.46	0.15	**0.04**	0.18
	*Biceps fem longus**	2.19	1.38	1.14	**0.04**	**0.00**	**0.04**
	Glut max mid	2.09	2.28	2.12	0.74	0.97	0.47
	Vastus med	0.88	1.69	1.65	0.09	0.07	0.66
	Vastus lat*	0.99	1.98	1.82	0.08	0.08	0.25
	*Gastroc med**	1.22	2.32	1.58	0.09	0.42	0.05
	Soleus*	1.73	4.85	4.22	**0.01**	**0.04**	0.30
	Tibialis ant*	3.32	0.21	0.29	**0.00**	**0.00**	0.15
	Ext digitorum	2.34	0.54	0.67	**0.00**	**0.00**	0.17
SS	Glut med ant	6.11	3.24	2.87	**0.00**	**0.00**	0.08
	Glut med mid*	2.62	1.64	1.39	**0.00**	**0.00**	**0.04**
	Glut med post	3.17	1.72	1.65	**0.00**	**0.00**	0.62
	Semimembranosis	0.85	1.72	1.46	**0.02**	0.08	0.09
	Biceps fem short	2.03	1.19	1.50	**0.01**	0.13	0.14
	Iliacus	2.75	1.43	1.36	**0.00**	**0.00**	0.53
	Psoas	3.61	1.78	1.69	**0.00**	**0.00**	0.54
	Rectus fem*	1.63	0.83	0.73	**0.02**	**0.00**	0.46
	*Gastroc med**	5.39	4.91	4.39	0.59	0.30	0.45
	Soleus*	12.32	8.82	9.55	**0.02**	0.14	0.43
	Tibialis post	1.80	2.54	2.55	0.14	0.11	0.97
TDS	Glut med ant	2.79	1.45	1.50	**0.02**	**0.02**	0.73
	Glut med post	1.52	0.43	0.53	**0.00**	**0.00**	0.19
	Iliacus	8.64	4.47	3.91	**0.00**	**0.00**	0.10
	Psoas	11.08	5.51	4.82	**0.00**	**0.00**	0.13
	Rectus fem*	2.34	1.28	1.07	**0.03**	**0.00**	0.13
	*Gastroc med**	4.32	1.55	1.62	**0.00**	**0.00**	0.82
	Soleus*	12.50	3.52	4.57	**0.00**	**0.00**	**0.04**
	Tibialis post	7.53	4.57	5.50	**0.04**	0.17	0.18
	Peroneus brev	5.16	2.33	2.97	**0.00**	**0.02**	0.07
SWING	*Semimeme branosis*	1.92	1.61	1.45	0.34	0.12	0.24
	Iliacus	2.19	1.65	1.55	0.10	**0.04**	0.17
	Psoas	2.56	1.81	1.70	**0.04**	**0.02**	0.15
	Soleus*	1.87	0.94	1.03	**0.00**	**0.01**	0.62
	Tibialis ant*	2.05	0.69	0.88	**0.00**	**0.00**	0.19
	Ext digitorum	2.18	1.25	1.11	**0.01**	**0.00**	0.36

IDS = Initial Double Support, SS = Single Stance, TDS = Terminal Double Support, EMGcon = EMG-constraint optimization.

compared to TD.

3.1. Clinical assessments

The CP children showed only a significant difference between pre- and post-measurements of CP-children for hip flexor MRC strength scores, which were significantly weaker after compared to before BTX-A treatment (Table 1). Ashworth spasticity scores showed a significant decrease in spasticity for the hip flexors, hip adductors and gastrocnemius muscles (Table 1).

3.2. Joint kinematics and kinetics

Joint kinematics were similar between patients pre- and post-BTX-A treatment (Fig. 1). Deviation in joint kinematics was only significantly decreased post-treatment for the ankle flexion angle. Larger differences were found in joint kinetics, with a significantly decreased deviation for hip, knee and ankle flexion (Fig. 1).

3.3. Modelled muscle forces

Table 2 only shows muscle forces for which the EMG-constrained force exceeded 1.5 N/kg. Results for all muscles in all phases of the gait cycle are presented in supplementary material (Table S2 till S5).

Muscle forces in CP children were significantly different compared to TD children, both before and after BTX-A treatment (Fig. 2). Towards the end of the stance phase, specifically iliacus, psoas and triceps surae muscle forces were lower for CP compared to TD children (Table 2). However, in other phases of the gait cycle, higher muscle forces in CP children were found, e.g. the triceps surae muscle forces in IDS. Differences before and after BTX-A treatment were limited, with only few significant differences between the pre- and post-BTX-A assessment (Table 2). When considering the whole muscle waveforms instead of single time points in the MPS (Fig. 3), most muscle forces were higher in CP than in TD children. The MPS additionally showed a small, but significant decrease for both the injected (from 0.59 N/kg pre-BTX-A to 0.53 N/kg post-BTX-A) and non-injected muscles (from 0.88 N/kg pre-BTX-A to 0.79 N/kg post-BTX-A).

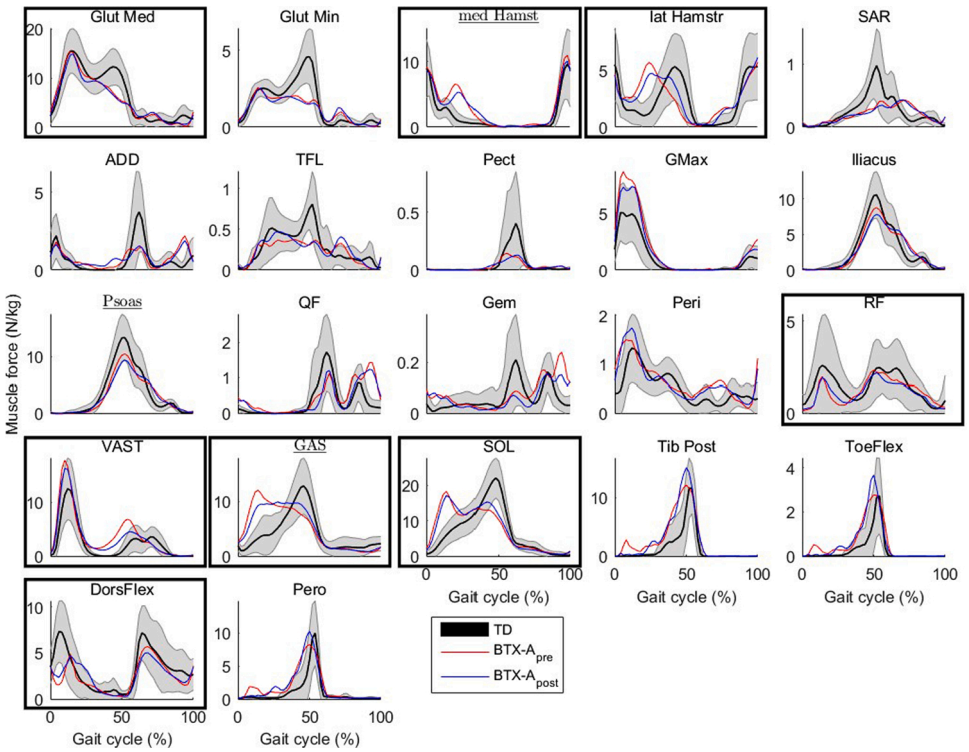

Fig. 2. Muscle forces calculated for all muscles in the model when using EMG constrained optimization. The black squares indicate the muscles for which EMG was measured, the underlined muscle names were injected with BTX-A.

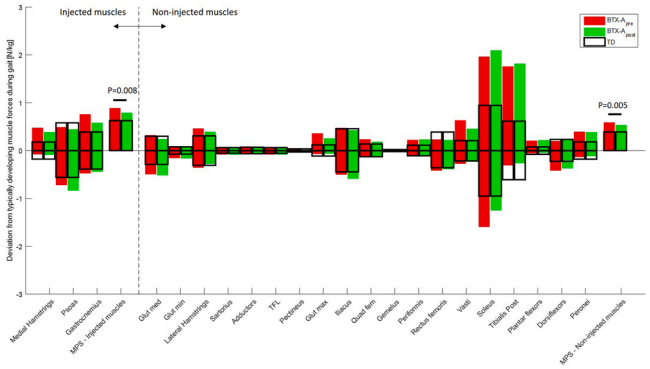

Fig. 3. The average Muscle-Force-Profile pre- (red bars) and post-BTX-A (green bars) for all participants with CP. Positive and negative Individual-Muscle-Score for the injected and non-injected muscles, as well as the Muscle-Profile-Score (MPS) for injected and non-injected muscles are shown. The MPS was calculated as the mean of the root-mean-square differences between the CP and average TD modelled muscle force waveforms over all analyzed individual muscles. The Individual-Muscle-Score was determined as the root-mean-square difference between the CP child's modelled muscle force waveform and the average waveform of the TD children. Since the Individual-Muscle -Score represents the variation over the gait cycle, values are both positive and negative. Black boxes re- present the average variation observed in typically developing (TD) children. The closer the bars are to the black boxes, the smaller are the deviations from the TD muscle forces. If the bars are within the black boxes, it indicates that the deviation of the CP children was less than the variation observed in the TD children (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

4. Discussion

This study showed that BTX-A injections only have a minor impact on dynamic modelled muscle forces during gait, despite reduced deviations in kinematics and kinetics. Nevertheless, spasticity was significantly reduced (improved Ashworth scores) after treatment for several major muscle groups, similar to previous research [26].

Observed changes in sagittal joint moments are not directly reflected in a change in individual muscle force, but a complex interaction across muscles is observed, thereby emphasizing the need to investigate individual muscle forces, rather than joint moments only. CP patients presented significantly different modelled muscle forces from TD children, both pre- and post-BTX-A treatment. For CP patients both before and after BTX-A treatment a reduced hip flexor moment at the end of stance, being related to reduced psoas forces; a reduced hip abductor moment during stance, being related to reduced gluteus medius forces and impaired initial contact due to excessive plantarflexor forces were found compared to TD children after BTX-A treatment. The average forces were significantly decreased after BTX-A compared to before treatment in only a few muscles, e.g. biceps femoris long head in IDS, gluteus medius in SS, and soleus in TDS (Table 2 and supplementary material), indicating no overall normalisation of the modelled muscle forces. Nevertheless the MPS, showed a significant decrease in the deviation of the modelled muscle forces from TD after BTX-A treatment for both the injected and non-injected muscles.

In clinics, BTX-A is used to slow down musculoskeletal impact of spasticity during young age and to optimize gait function till more skeletal maturity is reached. As such, it is expected that the complexity of future single event multi-level surgical (SEMLS) interventions can be impacted. In contrast, however, the present results suggest only a limited impact of BTX-A injections on the muscle force distribution during gait, impacting minimally musculoskeletal loading, especially compared to the impact of SEMLs [27]. Ongoing work using bone

growth simulations will need to confirm if the effect of BTX-A on musculoskeletal loading suffices to significantly contribute to the prevention of bony deformities.

The use of EMG constrained optimization affected the differences in muscle forces before and after the BTX-A treatment with most muscles presenting a small increase in force when imposing EMG constraints (supplementary material). Despite these differences in calculated muscle forces, the trends (increase or decrease in modelled muscle force) following BTX-A treatment, were unaltered by the optimization used. This indicates that, similar to what was reported by Kainz et al. [28], although the selected optimization approach will change individual modelled muscle force waveforms and magnitude, it will not change the overall conclusion on treatment effect.

This study includes several limitations. First, generic adult models scaled to the child's anthropometry were used, therefore no subject-specific geometry or muscle-tendon parameters were taken into account. In addition, subject-specific spasticity was not modelled. Although subject-specific models affect calculated muscle forces [17], the goal of this study was to determine the effect of BTX-A treatment, independent of the skeletal morphology. Second, to obtain a homogeneous group of CP subjects who received similar BTX-A treatment, a limited number of subjects was included in the study (14 CP and 10 TD children). This might affect the comparison of the treatment, specifically when p-values are near significance. Furthermore, calculated muscle forces might have been affected by differences in gait speed. However, differences in normalized walking speed were limited to the post-BTX-A condition. While decreased walking speed might explain partially muscle force differences, we opted to investigate the clinical impairments as they present, with decreased walking speed being an integral part of the pathological gait pattern and BTX-A impacting speed as part of the treatment outcome. Third, the morphological changes in CP children [29] and changes in the injected and neighbouring muscles as a result of the BTX-A treatment [30], were not taken into account in the models. Therefore, the modelled muscle forces might be overestimated, as affected muscles in CP children might not be able to produce the estimated level of force. In addition, diverse dynamical interactions between muscles were not taken into account.

In conclusion, the effect of BTX-A injections on modelled muscle forces during gait was only limited, despite differences in joint moments and clinical spasticity scores. Besides that, the use of EMG-constrained optimization is recommended when studying muscle balance in children with CP.

Role of the funding sources

This work was supported by the IWT-TBM [Grant number: 140184]. HK was funded by a H2020-MSCA individual fellowship [Grant number: 796120]. The funding sources had no involvement in the study.

Declaration of Competing Interest

The authors report no declarations of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.gaitpost.2020.08.122.

References

[1] V. Unnithan, J. Dowling, G. Frost, B. Volpe Ayub, O. Bar-Or, Cocontraction and phasic activity during gait in children with cp, Electromyogr. Clin. Neurophysiol. 36 (1996) 487–494, https://doi.org/10.1016/j.pcad.2015.11.006.

[2] S.K. Stackhouse, S.A. Binder-Macleod, S.C.K. Lee, Voluntary muscle activation, contractile properties, and fatigability in children with and without cerebral palsy, Muscle Nerve 31 (2005) 594–601, https://doi.org/10.1002/mus.20302.

[3] L. Van Gestel, H. Wambacq, E. Aertbeliën, P. Meyns, H. Bruyninckx, L. Bar-On, G. Molenaers, P. De Cock, K. Desloovere, To what extent is mean EMG frequency during gait a reflection of functional muscle strength in children with cerebral palsy? Res. Dev. Disabil. 33 (2012) 916–923, https://doi.org/10.1016/j.ridd.2011.12.010.

[4] H.K. Graham, P. Rosenbaum, N. Paneth, B. Dan, J.-P. Lin, D.L. Damiano, J. G. Becher, D. Gaebler-Spira, A. Colver, D.S. Reddihough, K.E. Crompton, R. L. Lieber, Cerebral palsy, Nat. Rev. Dis. Prim. 2 (2016) 15082, https://doi.org/10.1038/nrdp.2015.82.

[5] G. Molenaers, K. Fagard, A. Van Campenhout, K. Desloovere, Botulinum toxin A treatment of the lower extremities in children with cerebral palsy, J. Child. Orthop. 7 (2013) 383–387, https://doi.org/10.1007/s11832-013-0511-x.

[6] K. Desloovere, G. Molenaers, J. De Cat, P. Pauwels, A. Van Campenhout, E. Ortibus, G. Fabry, P. De Cock, Motor function following multilevel botulinum toxin type A treatment in children with cerebral palsy, Dev. Med. Child Neurol. 49 (2007) 56–61, https://doi.org/10.1111/j.1469-8749.2007.014xa.x.

[7] H.K. Graham, K.R. Aoki, I. Autti-Rämö, R.N. Boyd, M.R. Delgrado, D.J. Gaebler-Spira, M.E. Gormley, B.M. Guyer, F. Heinen, A.F. Holton, D. Matthews, G. Molenaers, F. Motta, P.J. García Ruiz, J. Wissel, Recommendations for the use of botulinum toxin type A in the management of cerebral palsy, Gait Posture 11 (2000) 67–79, https://doi.org/10.1016/s0966-6362(99)00054-5.

[8] D.H. Sutherland, K.R. Kaufman, M.P. Wyatt, H.G. Chambers, Injection of botulinum A toxin into the gastrocnemius muscle of patients with cerebral palsy: a 3-dimensional motion analysis study, Gait Posture 4 (1996) 269–279, https://doi.org/10.1016/0966-6362(95)01054-8.

[9] M. Galli, V. Cimolin, E.M. Valente, M. Crivellini, T. Ialongo, G. Albertini, Computerized gait analysis of botulinum toxin treatment in children with cerebral palsy, Disabil. Rehabil. 29 (2007) 659–664, https://doi.org/10.1080/09638280600948136.

[10] V.A. Scholtes, A.J. Dallmeijer, D.L. Knol, L.A. Speth, C.G. Maathuis, P.H. Jongerius, J.G. Becher, Effect of multilevel botulinum toxin a and comprehensive rehabilitation on gait in cerebral palsy, Pediatr. Neurol. 36 (2007) 30–39, https://doi.org/10.1016/j.pediatrneurol.2006.09.010.

[11] R.N. Boyd, V. Pliatsios, R. Starr, R. Wolfe, H.K. Graham, Biomechanical transformation of the gastroc-soleus muscle with botulinum toxin A in children with cerebral palsy, Dev. Med. Child Neurol. 42 (2010) 32–41, https://doi.org/10.1111/j.1469-8749.2000.tb00022.x.

[12] L.E.E. van der Houwen, V.A. Scholtes, J.G. Becher, J. Harlaar, Botulinum toxin A injections do not improve surface EMG patterns during gait in children with cerebral palsy-A randomized controlled study, Gait Posture 33 (2011) 147–151, https://doi.org/10.1016/j.gaitpost.2010.11.001.

[13] K.M. Steele, A. Seth, J.L. Hicks, M.H. Schwartz, S.L. Delp, Muscle contributions to vertical and fore-aft accelerations are altered in subjects with crouch gait, Gait Posture 38 (2013) 86–91, https://doi.org/10.1016/j.gaitpost.2012.10.019.

[14] K.M. Steele, A. Seth, J.L. Hicks, M.S. Schwartz, S.L. Delp, Muscle contributions to support and progression during single-limb stance in crouch gait, J. Biomech. 43 (2010) 2099–2105, https://doi.org/10.1016/j.jbiomech.2010.04.003.

[15] H. Kainz, M. Goudriaan, A. Falisse, C. Huenaerts, K. Desloovere, F. De Groote, I. Jonkers, The influence of maximum isometric muscle force scaling on estimated muscle forces from musculoskeletal models of children with cerebral palsy, Gait Posture 65 (2018) 213–220, https://doi.org/10.1016/j.gaitpost.2018.07.172.

[16] S.L. Delp, F.C. Anderson, A.S. Arnold, P. Loan, A. Habib, C.T. John, E. Guendelman, D.G. Thelen, OpenSim: Open source to create and analyze dynamic simulations of movement, IEEE Trans, Biomed. Eng. 54 (2007) 1940–1950, https://doi.org/10.1109/TBME.2007.901024.

[17] M. Wesseling, F. De Groote, L. Bosmans, W. Bartels, C. Meyer, K. Desloovere, I. Jonkers, Subject-specific geometrical detail rather than cost function formulation affects hip loading calculation, Comput. Methods Biomech. Biomed. Engin. 19 (2016) 1475–1488.

[18] D.G. Lloyd, T.F. Besier, An EMG-driven musculoskeletal model to estimate muscle forces and knee joint moments in vivo, J. Biomech. 36 (2003) 765–776, https://doi.org/10.1016/S0021-9290(03)00010-1.

[19] M. Sartori, J.W. Fernandez, L. Modenese, C.P. Carty, L.A. Barber, K. Oberhofer, J. Zhang, G. Handsfield, N.S. Stott, T.F. Besier, D. Farina, D.G. Lloyd, oward modeling locomotion using electromyography-informed 3D models: application to cerebral palsy, WIREs Syst. Biol. Med. (2017), e1368, https://doi.org/10.1002/wsbm.1368.

[20] K. Veerkamp, W. Schallig, J. Harlaar, C. Pizzolato, C.P. Carty, D.G. Lloyd, M. M. Van Der Krogt, The effects of electromyography-assisted modelling in estimating musculotendon forces during gait in children with cerebral palsy, J. Biomech. 92 (2019) 45–53, https://doi.org/10.1016/j.jbiomech.2019.05.026.

[21] V. Zatsiorsky, B. Prilutsky, Biomechanics of Skeletal Muscle, 1st ed., Human Kinetics Publishers, 2012.

[22] M.G.J. Gazendam, A.L. Hof, Averaged EMG profiles in jogging and running at different speeds, Gait Posture 25 (2007) 604–614, https://doi.org/10.1016/j.gaitpost.2006.06.013.

[23] R. Baker, J.L. McGinley, M.H. Schwartz, S. Beynon, A. Rozumalski, H.K. Graham, O. Tirosh, The gait profile score and movement analysis profile, Gait Posture 30 (2009) 265–269, https://doi.org/10.1016/j.gaitpost.2009.05.020.

[24] V. Cimolin, C. Condoluci, P.F. Costici, M. Galli, A proposal for a kinetic summary measure: the Gait Kinetic Index, Comput. Methods Biomech. Biomed. Engin. 22 (2019) 94–99, https://doi.org/10.1080/10255842.2018.1536750.

[25] A. Hof, Scaling gait data to body size, Gait Posture 4 (1996) 222–223.

[26] M. Galli, M. Crivellini, G.C. Santambrogio, E. Fazzi, F. Motta, Short-term effects of "Botulinum toxin A" as treatment for children with cerebral palsy: kinematic and kinetic aspects at the ankle joint, Funct. Neurol. (2001) 317–323.

[27] S. Van Rossom, H. Kainz, M. Wesseling, E. Papageorgiou, F. De Groote, A. Van Campenhout, G. Molenaers, K. Desloovere, I. Jonkers, Single-event multilevel surgery, but not botulinum toxin injections normalize joint loading in cerebral palsy patients, Clin. Biomech. Bristol Avon (Bristol, Avon) 76 (2020) 105025, https://doi.org/10.1016/j.clinbiomech.2020.105025.

[28] H. Kainz, H. Hoang, L. Pitto, M. Wesseling, S. Van Rossom, A. Van Campenhout, G. Molenaers, F. De Groote, K. Desloovere, I. Jonkers, Selective dorsal rhizotomy improves muscle forces during walking in children with spastic cerebral palsy, Clin. Biomech. 65 (2019) 26–33, https://doi.org/10.1016/j.clinbiomech.2019.03.014.

[29] R.O.D.S. Barrett, G.A. Lichtwark, Gross muscle morphology and structure in spastic cerebral palsy : a systematic review, Dev. Med. Child Neurol. 52 (2010) 794–804, https://doi.org/10.1111/j.1469-8749.2010.03686.x.

[30] M. Gough, C. Fairhurst, A.P. Shortland, Botulinum toxin and cerebral palsy : time for reflection? Dev. Med. Child Neurol. 47 (2005) 709–712.