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Acknowledgements

To graduate as master in Rehabilitation sciences and physiotherapy at the University of Hasselt, this thesis is one of the important requirements.

We want to sincerely thank Prof. dr. K. Klingels for the supervision, counseling and guidance during the process of this thesis. We also want to express our thanks to the junior researcher L. Brauers of the Rehabilitation centre Adelante (the Netherlands) for sharing her expertise and data. We are also very thankful for receiving data of the typically developing children from former master students K. Lemmens and D. Vanherk.

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Research context

This thesis fits in the research field of pediatric rehabilitation and is closely related to the neurological rehabilitation. Children with unilateral cerebral palsy (CP) have several motor impairments such as higher muscle tone, decreased muscle strength, decreased passive range of motion and selectivity problems (1, 2). Up to now, only limited research about muscle fatigue in the upper extremity in children with unilateral CP has been conducted. It might be hypothesized that muscle fatigue, described as the decrease of the maximal force or power capacity of a muscle over repeated or sustained contractions (3-5), plays a restrictive role on activity level in this population. Therefore, it is important to gain more insights in this phenomenon. The first aim of this study was to compare muscle fatigue during an isometric hand and pinch grip task between children with unilateral CP and typically developing children. The second aim was to determine whether muscle fatigue can be influenced by characteristics such as age, gender, Manual Ability Classification System (MACS)(6) level and maximal muscle strength.

The data of this study has been collected, statistically analyzed and processed by two students Rehabilitation Sciences and Physiotherapy of the University of Hasselt under supervision of promotor Prof. Dr. K. Klingels. The thesis fits within the research field of promotor Prof. Dr. K. Klingels on assessment and treatment of upper extremity function in pediatric populations. The research line on 'Muscle fatigue in children with unilateral CP' is a collaboration between REVAL Research Institute UHasselt (Prof. K. Klingels, Prof. P. Feys), Rehabilitation Centre 'Adelante' in Hoensbroek and Maastricht University (Dr. E. Rameckers, L. Brauers). This study also situates within the framework of the previous master thesis of K. de Koninck (Muscle fatigue during isometric grip tasks in adolescents with unilateral cerebral palsy) and the master thesis of K. Lemmens and D. Vanherk (Muscle fatigue index: reference values in typically developing children and adolescents).

The design of this study was developed by Prof. Dr. K. Klingels in collaboration with the two master students. Data of the typically developing children was received from the experiment of the master thesis of K. Lemmens and D. Vanherk. Data of the children with unilateral CP was received from the research project of the junior researcher L. Brauers and Dr. E. Rameckers of the Rehabilitation Centre 'Adelante' in Hoensbroek. The matching of the participants, the statistical analysis, processing and interpretation was done by the two master students. The

proofreading was executed by the promotor Prof. K. Klingels. The two master students also participated in another clinical study of the same research line of upper extremity function in pediatric populations: they participated in a two week therapy camp in Antwerp with constrained induced movement therapy (CIMT) and action observation therapy (AOT) for children with unilateral CP. Thereafter, they assisted the researchers of KULeuven with the clinical measurements of these children.

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Muscle strength and muscle fatigue during maximal isometric grip tasks in children with unilateral cerebral palsy

BACKGROUND: Until now, muscle fatigue in the upper extremity has not been investigated extensively in children with unilateral cerebral palsy (CP). Inconsistent findings in previous studies, differences in methodology and small sample sizes warrant further research.

OBJECTIVES: The first objective was to compare maximal hand and pinch grip strength and muscle fatigue between children with unilateral CP and typically developing (TD) children. Secondly, we aimed to investigate the influence on muscle fatigue of characteristics such as age, gender, Manual Ability Classification System (MACS) level and maximal muscle strength.

PARTICIPANTS: Sixty-one children with unilateral CP (33 males, 28 females; mean age 11y, SD 3y1m, range 7-16y) and 61 age and gender matched TD children were included.

MEASUREMENTS: In both hands, hand and pinch grip strength was measured with maximal isometric grip tasks. The muscle fatigue was calculated with the static fatigue index (SFI) based on a 30 seconds maximal isometric contraction.

RESULTS: Hand and pinch grip strength of the non-dominant hand (NDH) was in the CP group on average 47% and in the TD group 3% lower than in the dominant hand (DH) ($p \leq 0.006$). Hand grip strength in the DH and NDH was respectively 7% and 40% lower in children with CP compared to TD children ($p \leq 0.005$). The pinch grip strength in the NDH was 53% lower in children with CP in comparison with TD children ($p < 0.0001$), but in the DH a similar pinch grip strength was found between groups ($p = 0.46$). In the CP group, the SFI of hand and pinch grip was higher in the NDH compared to the DH ($p \leq 0.002$), except for the SFI of hand grip ($p = 0.567$). The SFI of hand and pinch grip was in both hands lower in the TD group compared to the CP group ($p < 0.0001$). The regression model showed that maximal muscle strength predicted 7% to 14% of the SFI, meaning that a higher maximal strength is related with lower muscle fatigue.

CONCLUSION: In general, children with unilateral CP have lower grip strength and higher muscle fatigue in comparison with TD children. Muscle weakness was the only predictive factor for higher muscle fatigue. Further research is warranted to optimize the measurement protocol of muscle fatigue and to investigate the influencing factors and underlying mechanism of muscle fatigue.

INTRODUCTION

"Cerebral palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication, behavior, by epilepsy and by secondary musculoskeletal problems" (7). Different subtypes of CP can be distinguished based on motor impairment: spastic, dyskinetic and ataxic CP (8). The spastic subtype CP may be either bilateral or unilateral spastic CP (8). The overall prevalence rate is one and a half to three in 1000 live births and 29% of these children have unilateral CP (8). In these children, the upper extremity is generally more affected than de lower extremity (9).

The International Classification of Functioning, Disability and Health (ICF) is a useful international standard to describe the impairments and limitations of the upper extremity on body function, activity and participation level. On body function level, children with unilateral CP have motor and sensory impairments (1). Motor impairments include higher muscle tone, decreased muscle strength, limitations in passive range of motion and selectivity problems. The mean relative grip strength of the affected hand compared to the non-affected hand is around 40% (2). Sensory dysfunction can affect up to 90% of the children with unilateral CP (10). On activity level, children with unilateral CP experience problems with reaching, grasping and releasing objects (11). These impairments and activity limitations influence each other and impact participation level (2, 12, 13).

The relation between impairments on body function level and activity limitations in children with unilateral CP has been investigated extensively. Clinical studies showed a strong relationship of distal muscle strength and distal muscle tone with unimanual capacity and bimanual performance (2, 12, 13). According to Klingels et al. (2012), the best predictors for unimanual capacity were distal strength, stereognosis and proprioception, while the best predictors for bimanual performance were wrist strength and grip strength (2). However, little is known about the relation between muscle fatigue and activity limitations in this population. Nevertheless, it might be hypothesized that muscle fatigue plays a restrictive role on activity level as most activities of daily require prolonged muscle activity such as cutting meat with a knife or carrying heavy objects.

Muscle fatigue can be described as the decrease of the maximal force or power capacity of a muscle over repeated or sustained contractions (3-5). A clear distinction must be made with the subjective feeling of generalized fatigue, which may be related to emotional, cognitive, physical, or biochemical processes (5). Muscle fatigue can be measured by surface electromyography (sEMG) and muscle fatigue indices. sEMG measures local muscle fatigue by recording myoelectric signals (biochemical and physiological changes in the muscle) during static and dynamic fatiguing tasks (14, 15). If the sEMG signal amplitude increases and the sEMG spectrum shifts toward lower frequencies during an isometric exercise, this is considered as muscle fatigue (14, 15). Muscle fatigue indices are also commonly used techniques for quantifying muscle fatigue. The Static Fatigue Index (SFI) is a regularly used index in studies with multiple sclerosis (MS) patients and is based on a 30 seconds sustained maximal isometric contraction (16, 17).

Until now, muscle fatigue in the upper extremity has not been investigated extensively in children with unilateral CP. Doix et al. (2013) investigated muscle fatigue in 12 children with CP and 17 typically developing (TD) peers with a submaximal isometric elbow flexion using the Biodex isokinetic dynamometer, EMG measures of the biceps and triceps brachii and accelerometers (18). These authors hypothesised that children with CP would have a longer endurance time because of three reasons. First of all, children with CP are weaker, and weaker individuals might be less fatigable than stronger individuals (19). Secondly, children with CP have relatively more slow type, fatigue resistant muscle fibres (20, 21). The third reason is because of an altered neural drive, children with CP recruit lesser motor units (MUs) during a maximal voluntary contraction (resulting in an underestimation of their muscle capacity) (22). Surprisingly, they found a similar endurance time between children with unilateral CP and the control group. This can be explained by the fact that children with CP, in contrast to TD children, cannot compensate muscle fatigue by the recruitment of additional MUs during a low-force level contraction (18). Leunkeu et al. (2010) reported similar findings for muscle fatigue of the quadriceps muscle (15). The EMG data suggested that muscle fatigue occurred sooner in children with CP, although there was no difference in time to exhaustion. The authors suggested that the difference between the results of the EMG data and the time to exhausting may be due to spasticity and co-contraction during maximal testing (15). However, van Meeteren et al. (2007) investigated muscle fatigue in young adolescents with unilateral CP using a sustained maximal isometric contraction, measured by a handgrip dynamometer (23).

The SFI was used to calculate the muscle fatigue, defined as the decrease of maximal strength over time (16, 17). These authors reported that muscle fatigue of the affected hand did not differ significantly with the non-affected hand in young adults with CP, but the muscle fatigue of both the dominant and non-dominant hand was significantly lower in comparison with controls (23).

The inconsistent findings in previous studies, differences in methodology and small sample sizes warrant further study in the area of muscle fatigue in children with unilateral CP. The first aim of this study was therefore to compare muscle fatigue during an isometric grip and pinch task between children with unilateral CP and TD children. The second aim was to determine whether muscle fatigue can be influenced by characteristics such as age, gender, Manual Ability Classification System (MACS) (6) level and maximal muscle strength.

This study will provide deeper insights into the phenomenon of muscle fatigue in children with unilateral CP, which may result in optimizing treatment advice.

MATERIAL AND METHODS

Participants

Children with unilateral CP aged between 7 and 16 years were included, in case they were capable and cooperative to participate in the testing protocol. Exclusion criteria were 1) upper extremity surgery during the last six months or 2) botulinum toxin-A injections during the last six months prior to the testing. TD children were matched for age (range within one year) and gender with the children with unilateral CP. TD children were excluded in case of known chronic neurological, cardiovascular, respiratory or musculoskeletal disorders.

In this cross-sectional study, data was used from rehabilitation centres of the Netherlands (Adelante, Valkenburg). Data collection started in January 2014 and continued till October 2016. Between October 2014 and February 2016 data were collected from 118 TD children between seven and 16 years old from Flemish schools and youth movements.

For the children with unilateral CP, the study was approved by the Medical Ethical committee of Maastricht University (015095). For the TD children the study was approved by the Medical Ethical committee of the University Hospital of Leuven and the Hasselt University (S57029, ML11069).

Protocol

The children with CP were tested by six physical therapists, trained by dr. E. Ramaekers and the TD children were tested by two physical therapy students.

The maximal hand grip and pinch grip strength and a 30 seconds isometric endurance task were assessed with a digital Jamar dynamometer (E-link, Biometrics Ltd, Newport, UK). The participant was seated in a chair with back support, the feet flat on the ground, the elbow in 90° flexion and the forearm supported on the table. The forearm was placed in a neutral position between pronation and supination and the wrist between flexion and extension. The forearm was fixated by the assessor. First the dominant or non-affected hand was tested and thereafter the non-dominant or affected hand. For measuring the hand grip strength, the handle of the digital Jamar dynamometer (E-link, Biometrics Ltd, Newport, UK) was adjusted to the hand size. For measuring the pinch grip strength, the biometric's pinch meter was used. The thumb of the participant was placed on the sensor side and digit II, III, IV and V on the back

of the biometric's pinch meter. For measuring the maximal hand grip and pinch grip strength, the participant was asked to squeeze as hard as possible for three seconds. After 30 seconds of rest, a second maximal strength test was performed. Three measurements were performed. If these measurements differed more than 20%, one additional measurement was performed.

For the isometric endurance task, the participant had to perform a maximal contraction for 30 seconds. The instruction was: "Ready to squeeze, three, two, one and squeeze". The participants were verbally motivated and received feedback about the remaining time to squeeze during the test.

Primary outcomes

The primary outcome measures of this study were maximal muscle strength and muscle fatigue.

a) The maximal muscle strength

The mean maximal hand grip and pinch grip strength in kilograms was calculated from the three most consistent test results from the digital Jamar dynamometer (E-link, Biometrics Ltd, Newport, UK) and the biometric's pinch meter. Allen & Barnett (2011) established the concurrent validity and test-retest reliability of the Biometrics E-LINK EP9 electronic dynamometer in 49 healthy participants. They found excellent validity and test-retest reliability (23). In children with unilateral CP (5-15 years), Klingels et al. (2010) showed good to excellent interrater and test–retest reliability for the Jamar dynamometer (24). Mathiowetz et al. (1984) evaluated the reliability and validity of hand strength tests in 27 college women. They found a good to excellent inter-rater reliability for both grip and pinch strength (25).

b) The muscle fatigue

Muscle fatigue during a 30 seconds sustained maximal isometric contraction was calculated by the Static Fatigue Index (SFI).

Firstly, the maximal hand grip strength and the time to this maximal hand grip strength (T_{max}) was noted. Secondly, the hypothetical area under de curve (HAUC) was calculated by

multiplying the maximal hand grip strength (in kilograms) by 30 minus T_{max}. The HAUC was the curve acquired when the subject held the maximal strength constantly during 30 seconds. Thereafter, the actual area under the curve (AUC) was calculated by the area under the strength time curve from T_{max} to 30 seconds. The formula to calculate the SFI is: 100%*[1–(AUC/HAUC)] (figure 1) (16, 17). The same calculation was made for the muscle fatigue of the pinch grip.

A pilot study of junior researcher Lieke Brauers evaluated the use of the SFI in children with CP and found excellent test-retest reliability for the SFI of pinch grip and a good test-retest reliability for the SFI of hand grip. Swid et al. (1999) investigated the fatigue index estimated as the area under the curve using a a 30 seconds sustained maximal grip task and found a good to very good test-retest reliability in patients with MS (26). The validity has not been described yet.

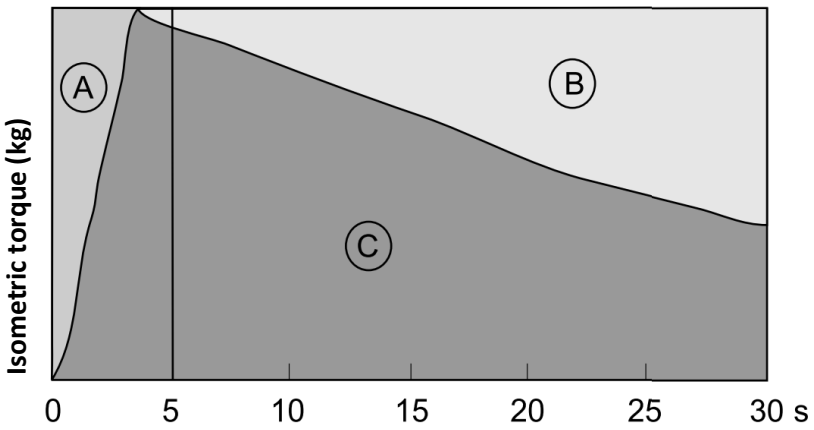

Figure 1: Strength time curve during a 30 seconds sustained maximal isometric contraction. A = T_{max}, B = HAUC, C = AUC (16)

Secondary outcomes

Descriptive data from the TD children were age, gender and hand preference. Descriptive data from the CP children were age, gender, hand preference and MACS-level.

Statistical analysis

Descriptive statistics were calculated to describe the results of age, gender and hand preference in both groups and MACS-levels in children with CP. After logarithmic transformation, the maximal strength was normally distributed. As the SFI had a normal

distribution, parametric statistics were used for both outcome variables. For comparison between matched groups and within groups (between dominant and non-dominant hand) paired t-tests were used. Significance was accepted at a p-value calculated according to the Holm-Bonferroni Method (Target α / (n – rank + 1). Target α was 0.05. Therefore a significant p-value ranged from 0.003 to 0.05.

An independent samples t-test was run in both groups to investigate whether the mean SFIs differed by gender. Pearson correlation coefficients were calculated between SFI and age and between SFI and the logarithm of maximal strength in both groups. The Spearman's rho correlation coefficient was calculated between SFI and MACS in children with CP. Significance was accepted at $p \leq 0.05$ and the following cut-off values were used for the interpretation of the correlations: 0.00 to 0.25 little or no relationship, 0.25 to 0.50 fair relationship, 0.50 to 0.75 moderate to good relationship and above 0.75 good to excellent relationship (26).
A forward stepwise multiple regression analysis was executed to identify which factors explained the SFI in both groups. Predictor variables were gender, MACS (only in children with CP), the logarithm of the maximal hand or pinch grip force of the affected or non-affected hand. Because of multicollinearity age was not included in the model. The criterion for entry into the model was $p<0.05$ and for removal $p>0.15$. All statistics were performed using IBM SPSS Statistics V22.0 software.

RESULTS

Participants

In total, 122 children were included in the study: 61 children with unilateral CP and 61 age and gender matched TD children, of which 28 girls and 33 boys. Mean age was 11 years (standard deviation 3 years 1month; range from 7 to 16 years). The majority of children with unilateral CP had a MACS-level I or II (respectively 20 and 28) and 13 children had a MACS-level III. In the CP group 33 children were left-handed and 28 right-handed, in the TD group nine children were left-handed and 52 right-handed.

Maximal strength

Table I and figure 1 show the means and standard deviations (SD) of the logarithmic scores of maximum strength for both hands in children with CP and TD children. The logarithm of maximum hand and pinch grip strength of the non-dominant hand was in the CP group on average 47% lower than in the dominant hand ($p < 0.0001$) and in the TD group 3% lower ($p \leq 0.006$).

The logarithm of maximum hand grip strength of the dominant and non-dominant hands were respectively 7% and 40% lower in children with CP than in TD children ($p \leq 0.005$). This significant difference was also found for the logarithm of maximum pinch grip strength of the non-dominant hand which was 53% lower in children with CP than in TD children ($p < 0.0001$). The logarithm of maximum pinch grip strength of the dominant hand did not differ significantly between groups ($p = 0.46$).

Static fatigue index

Table I and figure 2 show the SFI for both hands in children with CP and TD children. In the TD group, the SFI of hand grip of the dominant hand was significantly lower (mean 39%, SD 8.6) than in the non-dominant hand (mean 42%, SD 7.8) ($p = 0.001$). In the CP group there was no difference between the dominant and non-dominant hand (respectively mean 56%, SD 14.6 and mean 57%, SD 15.4; $p = 0.567$). In both groups, the SFI of pinch grip was significantly lower in the dominant hand (respectively mean 36%, SD 7.0 and mean 54%, SD 15.4) than in the non-dominant hand (respectively mean 39%, SD 8.9 and mean 64%, SD 16.1) ($p \leq 0.002$).

A significantly lower SFI of hand grip was found for the TD children compared to the CP children in both dominant (respectively mean 56.3%, SD 14.6 and mean 39.1%, SD 8.6) ($p <$

0.0001) and non-dominant hands (respectively mean 57.3%, SD 15.4 and mean 42.2%, SD 7.8) ($p < 0.0001$). For the SFI of pinch grip, the same difference was found between children with CP and TD children ($p < 0.0001$). The corresponding SFI values were respectively 54.1% (SD 15.4) for the dominant hand and 63.7% (SD 16.1) for the non-dominant hand in children with CP and 35.7% (SD 7.0) for the dominant hand and 39.0% (SD 8.9) for the non-dominant hand in TD children.

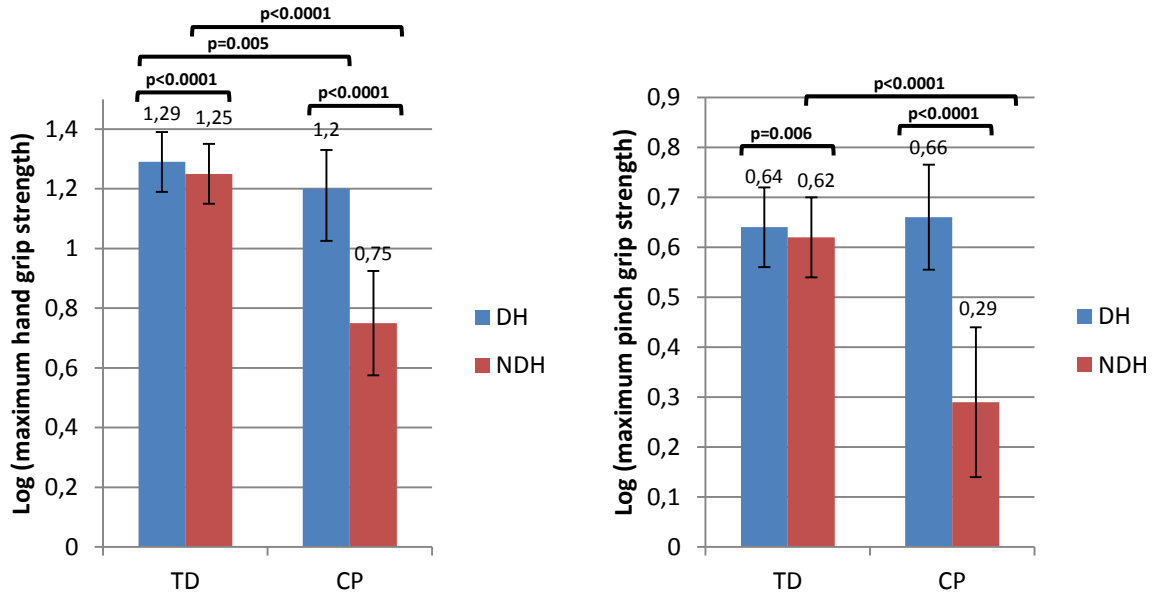

Figure 1: Mean values and standard deviation of the Logarithm of the maximal hand and pinch grip strength. Log: Logarithm, TD: typically developing, CP: cerebral palsy; DH: dominant hand; NDH: non-dominant hand.

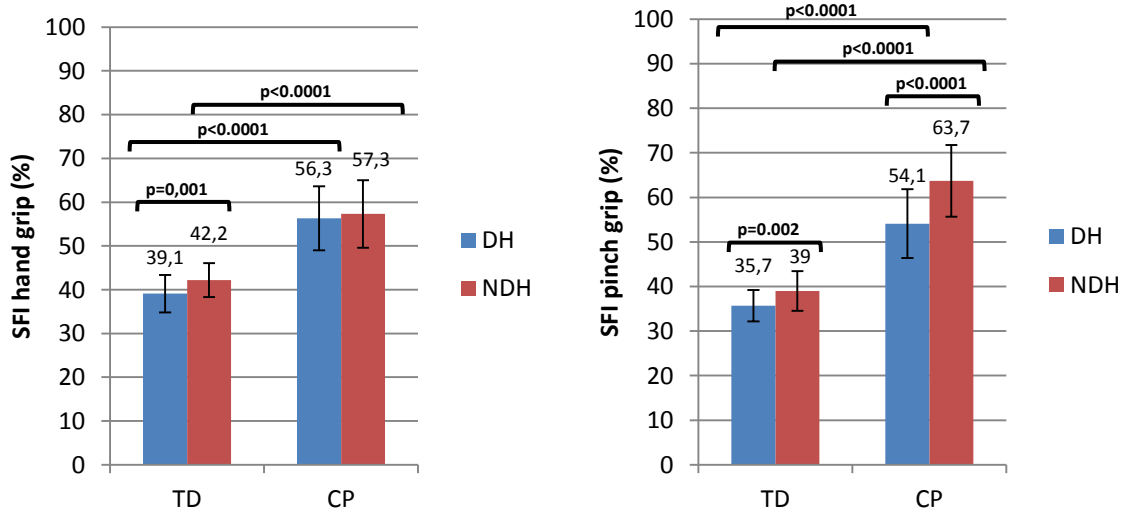

Figure 2: Mean values and standard deviation of the static fatigue index of the hand and pinch grip strength. TD: typically developing, CP: cerebral palsy; DH: dominant hand; NDH: non-dominant hand; SFI: static fatigue index.

Table I: Logarithm of maximum strength and SFI for both dominant and non-dominant hand in children with CP and TD children

Log(maximum strength) (mean (SD))						
Grip	CPAH	CPNAH	p-value	TDNDH	TDDH	p-value
Hand	0.75 (0.35)	1.20 (0.26)	<0.0001*	1.25 (0.20)	1.29 (0.20)	<0.0001*
Pinch	0.29 (0.30)	0.66 (0.21)	<0.0001*	0.62 (0.16)	0.64 (0.16)	0.006*
	CPNAH	TDDH	p-value	CPAH	TDNDH	p-value
Hand	1.20 (0.26)	1.29 (0.20)	0.005*	0.75 (0.35)	1.25 (0.20)	<0.0001*
Pinch	0.66 (0.21)	0.64 (0.16)	0.460	0.29 (0.29)	0.62 (0.16)	<0.0001*
SFI (mean (SD))						
Grip	CPAH	CPNAH	p-value	TDNDH	TDDH	p-value
Hand	57.3 (15.4)	56.3 (14.6)	0.567	42.2 (7.8)	39.1 (8.6)	0.001*
Pinch	63.7 (16.1)	54.1 (15.4)	<0.0001*	39.0 (8.9)	35.7 (7.0)	0.002*
	CPNAH	TDDH	p-value	CPAH	TDNDH	p-value
Hand	56.3 (14.6)	39.1 (8.6)	<0.0001*	57.3 (15.4)	42.2 (7.8)	<0.0001*
Pinch	54.1 (15.4)	35.7 (7.0)	<0.0001*	63.7 (16.1)	39.0 (8.9)	<0.0001*

CPAH: Cerebral Palsy Affected Hand; CPNAH: Cerebral Palsy Non-Affected Hand; SD: Standard Deviation; SFI: Static Fatigue Index; TDDH: Typically Developing Dominant Hand; TDNDH: Typically Developing Non-Dominant Hand;*significant p-values according to Holm-Bonferroni value (explanation see methods).

Correlations

Table II and III display the correlations between SFI and age, MACS and maximal hand muscle strength in TD children and children with CP.

In the TD group, there was no significant difference between the SFIs of boys and girls in the dominant and non-dominant hand ($p=0.10$ to 0.80). Fair to moderate negative correlations were found between age and the SFI of pinch grip of both hands and hand grip of the non-dominant hand in TD children: older children showed less muscle fatigue compared to younger children ($r=-0.27$ to -0.50; $p\leq0.036$). The logarithms of the maximal pinch and hand grip strength of the non-dominant hand were fairly correlated with respectively the SFI of pinch grip and the SFI of hand grip of the non-dominant hand ($r=-0.35$ to -0.37; $p\leq0.006$). No correlations were found for the dominant hand. The correlations of the SFIs of pinch grip or hand grip between both hands were moderate to good ($r=0.56$ to 0.64; $p<0.0001$). Furthermore, a fair correlation was found between SFI of pinch grip and the SFI of hand grip in the dominant and in the non-dominant hand ($r=0.43$ to 0.46; $p\leq0.001$).

In the CP group, there was no significant difference between the SFIs of boys and girls in the dominant and non-dominant hand ($p= 0.09$ to 0.94). A fair negative relationship was found between age and the SFIs of pinch grip in both hands ($r=-0.27$ to -0.35; $p<0.035$). There was no correlation between MACS and SFIs. The logarithm of the maximal muscle strength showed a fair correlation with the SFIs of pinch grip in both hands and the SFI of hand grip in the affected hand ($r=-0.31$-0.37; $r\leq0.016$). The correlations of the SFIs of pinch grip or hand grip between both hands were moderate to good ($r=0.62$ to 0.66; $p<0.0001$). Also, a moderate to good correlation was found between SFI of pinch grip and the SFI of hand grip in the non-affected and in the affected hand ($r=0.49$ to 0.49; $p\leq0.001$).

Table II : Correlations between SFI for both dominant and non-dominant hand and age and maximal hand muscle strength in TD children

	TD-group (n=61)			
	SFI Pinch grip NDH correlation coefficient p-value	**SFI Pinch grip DH** correlation coefficient p-value	**SFI Hand grip NDH** correlation coefficient p-value	**SFI Hand grip DH** correlation coefficient p-value
Age	-0.50[p] <0.0001	- 0.27[p] 0.036	-0.31[p] 0.015	-0.21[p] 0.099
Log(max pinch grip strength NDH)	-0.37[p] 0.003			
Log(max pinch grip strength DH)		-0.11[p] 0.400		
Log(max hand grip strength NDH)			-0.35[p] 0.006	
Log(max hand grip strength DH)				-0.22[p] 0.095
SFI Pinch grip NDH		0.56[p] <0.0001	0.43[p] 0.001	
SFI Pinch grip DH				0.46[p] <0.0001
SFI Hand grip NDH				0.64[p] <0.0001

DH: dominant hand; Log(): Logarithm of(); ND: non-dominant hand; r^p= Pearson correlation coefficient; SD: Standard Deviation; SFI: Static Fatigue Index; TD: Typically Developing

Table III: Correlations between SFI for both affected and non-affected hand and age, MACS and maximal hand muscle strength in children with CP

	CP-group (n=61)			
	SFI Pinch grip AH correlation coefficient p-value	**SFI Pinch grip NAH** correlation coefficient p-value	**SFI Hand grip AH** correlation coefficient p-value	**SFI Hand grip NAH** correlation coefficient p-value
Age	- 0.27[p] 0.035	- 0.35[p] 0.005	-0.14[p] 0.300	-0.02[p] 0.909
MACS	0.17[s] 0.184	-0.08[s] 0.535	0.02[s] 0.853	0.02[s] 0.875
Log(max pinch grip strength AH)	-0.31[p] 0.016			
Log(max pinch grip strength NAH)		-0.33[p] 0.009		
Log(max hand grip strength AH)			-0.37[p] 0.004	
Log(max hand grip strength NAH)				-0.22[p] 0.093
SFI Pinch grip AH		0.66[p] <0.0001	0.59[p] <0.0001	
SFI Pinch grip NAH				0.49[p] <0.0001
SFI Hand grip AH				0.62[p] <0.0001

AH: affected hand; CP: cerebral palsy; Log(): logarithm of (); NA: non-affected hand; r^p= Pearson correlation coefficient, r^s= Spearman's rho correlation coefficient; SD: Standard Deviation; SFI: Static Fatigue Index.

Multiple regression analysis

In TD children, the multiple regression model which best predicted the SFI of hand grip of the non-dominant hand included the logarithm of the maximal hand grip strength of the non-dominant hand (R^2 = 12%, p=0.006). There was no predictor variable included in the model that contributed to the model for the SFI of hand grip of the dominant hand. The multiple regression model which best predicted the SFI of pinch grip of the non-dominant hand in TD children included only one variable: the logarithm of the maximal pinch grip strength of the non-dominant hand (R^2 = 14%, p=0.006)

In children with CP, the multiple regression model which best predicted the SFI of hand grip of the affected hand included the logarithm of the maximal hand grip strength of the affected hand (R^2 = 14%, p= 0.004). There was no predictor variable included in the model that contributed to the model for the SFI of hand grip of the non-affected hand. The multiple regression model which best predicted the SFI of pinch grip of the affected hand and the non-affected hand in children with CP included only one variable: the logarithm of the maximal pinch grip strength of the affected hand (R^2 = 9%, p= 0.016) and non-affected hand (R^2=11%, p=0.009). Sex and MACS level did not contribute to the models of SFI.

DISCUSSION

This study compared the maximal muscle strength and muscle fatigue during an isometric grip and pinch task between 61 children with unilateral CP and 61 TD children, matched for age and gender. Secondly, the influence on muscle fatigue by characteristics such as age, gender, MACS-level and maximal muscle strength was investigated.

The maximal hand and pinch grip strength was lower in the non-dominant hand in comparison with the dominant hand. In the TD group, the dominant hand was only 3% stronger, whereas in the CP group the non-affected hand was 47% stronger. This was expected because of the motor impairments reported in the affected side in the CP group. Klingels et al. (2012) found that the mean relative grip strength in the affected hand was 60% lower than in the non-affected hand in a study with 81 children with unilateral CP aged 5-15 years (2). Van Meeteren et al. (2007) found that the maximal grip strength of the involved hand in young adults with unilateral CP was approximately 50% of the uninvolved hand. In the group of healthy subjects, they found that the maximal grip strength of the non-dominant hand was 88% of the dominant hand (23). Tomhave et al. (2015) compared the hand and pinch grip strength of 37 children with unilateral CP between both hands and with age-matched norms. They found a 60% stronger grip strength and 32% stronger pinch strength in the non-affected hand (27).

In this study, maximal hand grip strength in the TD group in the dominant and non-dominant hand was respectively 7% and 40% higher compared with the CP group. This difference was also found for the maximal pinch grip strength in the non-dominant hand (53% higher in the TD group), but was not found in the dominant hand. Tomhave et al. (2015) also found a lower hand and pinch grip strength in the affected hand of children with unilateral CP in comparison with normative values for the non-dominant hand. However, they found that the hand and pinch grip strength in the dominant hand of children with CP was similar to age-normative values of TD children (27). Van Meeteren et al. (2007) found a difference for the maximal grip strength between young adults with CP and healthy subjects, both for the dominant and non-dominant hand (23). These results suggest that the non-affected hand may also be impaired in persons with unilateral CP (23), which could be due to several reasons. First, in a study of Brown et al. (1989) 50% of the children with a unilateral lesion had a bilateral impairment (29). The authors suggested that this could be caused by the 10-30% of the fibers of the lateral corticospinal tract that stays uncrossed (28). Secondly, a bilateral brain lesion in the children of

our study cannot be ruled out completely. In previous studies, up to 40% of children diagnosed with unilateral CP, had a bilateral lesion (29-31). This could cause an impaired muscle coordination of both sides (23, 32). Thirdly, lesions in one hemisphere will typically result in changes in hemispheric dominance (i.e. lesions in the right hemisphere will typically result in right-handedness and vice versa). However, it is not clear if the children in this study were naturally left- or right-handed because of their genetic predisposition or that their handedness was influenced because of the brain damage (33, 34). Following these hypotheses, the 'less affected hand' instead of the 'non-affected hand' would be a more appropriate term for people with unilateral CP.

In this study, the SFI was measured during a 30 seconds isometric endurance task. In the CP and TD group, the SFI of hand and pinch grip was lower in the dominant hand compared with the non-dominant hand, except for the SFI of hand grip in the CP group. The latter finding is in line with the study of van Meeteren et al. (2007): they found no significant difference for the muscle fatigue of hand grip between both hands in young adults with CP (23). Muscle fatigue was also measured with the SFI, based on a maximal isometric contraction over a 20 seconds period. However in the healthy subjects of their study, they did not find a difference for the muscle fatigue between both hands. Another study found that in healthy adults the dominant hand was stronger, but also fatigued more rapidly than the non-dominant hand (35).

Between groups, the TD group had a significantly lower SFI of hand and pinch grip for both hands. This is in line with the study of van Meeteren et al. (2007): they found for both hands a difference for the SFI between young adults with CP and healthy subjects (23). In contrary, another study about the muscle fatigue in the upper extremity found no difference in time to task failure, EMG median frequencies and acceleration fluctuations between 12 children with CP and 17 TD children during a submaximal isometric elbow flexion task. Moreover, they did find an increment of EMG amplitude in the TD children, but not in children with CP. Their findings might indicate that during sustained low force contractions children with CP, in contradiction with TD children, do not compensate muscle fatigue with recruitment of additional motor units (18). Studies about the muscle fatigue in the lower extremity in children with CP are not consistent with each other. This could be partly due to differences in the measurements of muscle fatigue. Eken et al. (2014) stated some limitations of a maximal isokinetic voluntary fatigue protocol. Because people with CP are not able to maximally recruit

their muscles, a maximal voluntary contraction could result in an underestimation of their muscle capacity and could therefore delay fatigue in such protocols (21, 22, 36). Indeed, studies using such maximal isokinetic voluntary fatigue protocol did find a better muscle endurance in people with CP in comparison with TD people (36-38). Some of these authors explained that the lower muscle fatigue in people with CP could be due to morphological muscle adaptations, such as selective type II fiber atrophy and type I fiber predominance (22, 38-43). Studies using a submaximal fatigue protocol did find a higher or similar muscle fatigue in children with CP in comparison with TD children (15, 36, 44). All these studies investigated the muscle fatigue of the knee extensors and/or flexors (15, 36-38, 44, 45). However, these contrasting findings about muscle fatigue in the lower extremity in children with CP may also be due to other reasons such as the small sample sizes of the studies or other (un)known influencing factors on muscle fatigue.

In this study, the relations between SFI and gender, age, MACS and maximal strength were also investigated. No difference in muscle fatigue was found between boys and girls and gender did not contribute to the regression model. In line with this finding, previous research did not find a difference of the muscle fatigue in the lower extremity between TD males and females (46-48). Age had a fair correlation with the SFI of the hand and pinch grip of the non-dominant hand and with the SFI of pinch grip in the dominant hand in the TD group and with the SFI of pinch grip of both hands in the CP group. As the correlations were negative, a higher age was correlated with lower muscle fatigue. However, in this study the range of ages was only from seven to 16 years. Dipla et al. (2009) investigated the fatigue resistance in healthy persons during high–intensity exercise and found a gradual decline from childhood to adulthood in males, while females would establish the adult profile at mid-puberty (14-15years)(47). A meta-analysis about age-related differences in muscle fatigue in TD adults reported a better fatigue resistance with advancing age (≥55 years in comparison with 18-45 years) for both sustained and intermittent isometric contractions, but not for isokinetic contractions (46). A greater proportion of type I or slow, oxidative fibers could be a possible explanation for the lower muscle fatigue in older adults (46).

The maximal hand grip strength of the non-dominant hand was both in the CP and TD group fairly correlated with the SFI of hand grip in the non-dominant hand. The same was found for the maximal pinch grip strength. In the CP group, the maximal pinch grip strength of the

dominant hand was also fairly correlated with the SFI of pinch grip in the same hand. The same variables of maximal strength that were correlated with the SFI, were also the only contributing factors in the regression model with a predictive value varying from 7% to 14%. However, the correlations of the maximal strength with the SFI were negative correlations, meaning that a higher maximal strength was correlated with a lower muscle fatigue. This is not in line with previous research. In healthy adults, Meldrum et al. (2007) did not find a correlation between the SFI and maximum hand grip strength, measured by a maximum voluntary isometric contraction of the hand grip (49). Eken et al. (2013) investigated muscle fatigue in the knee flexors and extensors and stated that the lower fatigue in children with CP coincides with lower maximal muscle strength, in contrast to this study (45).

Beside differences in the measurements of the SFI, as described above, the specific muscle groups investigated in studies and the influence of co-contraction and spasticity can also play a role in the inconsistencies among different studies about muscle fatigue. Moreau et al. (2016) investigated the muscle fatigue in the knee extensors and flexors by calculating the normalized percentage decline in peak torque and rate of decline with a repeated maximal concentric knee extension and flexion protocol (37). The rate of decline in peak torque for the knee extensors was lower in the CP group than in the TD group. Moreover, between the two groups, they found a similar decline in agonist EMG, but a greater decline in antagonist EMG in the CP group. They stated that this decrease of antagonist activity and thus decrease of the relative opposing force, could be the cause of a lesser decline in net torque in comparison with the TD group. Interestingly, they did not find such a difference in torque data between groups during flexion (37). The fact that the knee and wrist flexors are tend to show more spasticity and co-contraction in comparison with the knee and wrist extensors, might be an explanation why these former muscle groups did not show a lower muscle fatigue in children with unilateral CP in comparison with TD children (8).

There are some limitations in this study. First, there is a lack of uniformity about the definition, measurement protocol and calculations of muscle fatigue. This hinders comparison with previous studies. Some authors stated that a sustained maximal voluntary contraction, as used in this study, is the ‘gold standard’ for measuring muscle fatigue (50). However, there is no standard for analyses to calculate the muscle fatigue. Although there is some evidence for the reliability of the SFI (16, 17, 51), there is a scarcity of evidence for the use of the SFI in children

with unilateral CP. A further disadvantage about the SFI is that strength-time curves (obtained from the sustained maximal isometric contraction) from different children can be different in shape but still have the same value calculated from the formula. Therefore, it should be recommended to include the force generation delay and force variability in the fatigue calculation in order to be able to quantifiably measure every part of the strength-time curve. Another disadvantage is that the method to measure muscle fatigue does not provide information about the underlying mechanism of the fatigue. It is for example impossible to differentiate between central of peripheral muscle fatigue. Also, from the included children in this study, there was no data available about spasticity, although evidence has already stated its relation with muscle fatigue. Moreau et al. (2008) investigated the contributing factors of muscle fatigue in 18 subjects with CP (mean age 17 years). They found that, in order of loadings, the strongest predictors of the lower rate of hamstring fatigue were greater hamstring co-contraction, spasticity and weakness. The strongest predictors of greater quadriceps fatigue were greater quadriceps co-contraction and strength (38).
Future research should optimize the measurement protocol of muscle fatigue in children with unilateral CP and studies should include influencing factors such as spasticity and co-contraction. Because of the potential link between muscle fatigue and activities of daily living, future research can investigate possible relations of muscle fatigue with factors on activity level, such as unimanual capacity and bimanual performance. Such insights are clinically interesting because of the potential to optimize the therapy of these children.

In conclusion, this is the first study with a large sample size of 122 children investigating the maximum muscle strength and muscle fatigue of the hand and pinch grip in children with unilateral CP and TD children. Maximal muscle strength was in both groups higher in the dominant hand and was (except for the pinch strength in the dominant hand) higher in the TD group than the CP group. Muscle fatigue was in both groups higher in the non-dominant hand, except for the muscle fatigue of the hand grip in the CP group. Between both groups, muscle fatigue was higher in the CP-group, both for hand and pinch grip and for both the dominant and non-dominant hand. The regression model revealed that only 7% to 14% of the muscle fatigue can be predicted by the maximal muscle strength of the same muscle group. Further research is warranted to optimize the measurement protocols of muscle fatigue and to investigate the influencing factors and underlying mechanism of muscle fatigue.

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