**A pilot study of proximal strength training in Charcot-Marie-Tooth disease**

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**Abstract**

Gait analysis of people with Charcot-Marie-Tooth (CMT) disease revealed

proximal adaptive gait strategies to compensate for foot drop.We previously demonstrated

that hip flexor muscle fatigue can limit walking endurance. This pilot study used a

single-blinded cross over design to investigate the effect of a 16-week home-based

programme of resistance training on hip flexor muscle strength. Measures of walking

endurance, gait speed, exertion, fatigue, and general activity were also recorded. The

exercise protocol was based on American College of Sports Medicine recommendations.

A mixed effects model was used for analysis. Twenty-six people finished the study, with

average reported exercise participation of 93%. No negative effects of exercise were

observed. Significant increase in hip flexor muscle strength was observed on the left, but

not the right. No changes were observed in walking speed and endurance measures. This

pilot study of home-based resistance training showed a modest improvement in hip strength

but only on one side. The lack of a more significant improvement and no improvement in

walking measures suggests that this training protocol may not be optimal for people with

CMT and that patients may need to stratified differently for training studies in CMT.

*Key words:* endurance, exercise, gait, proximal muscles, resistance traininig, walking

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***Introduction:***

*This study was funded by a grant from the Muscular Dystrophy Campaign (RA2/782/1). M.M.R. is grateful to the Medical Research Council (MRC) for their support. M.M.R. is grateful for a grant support from the NINDS/ORD (1U54NS065712-01). This work was undertaken at University College London Hospitals/University College London, which received a proportion of funding from the Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme.* We conducted a pilot study investigating the effects of resistance training of specifically the hip flexor muscles in people with Charcot Marie Tooth (CMT) disease. A biomechanical gait analysis has shown that proximal compensatory movement strategies around the hip are employed by people with CMT to compensate for distal weakness (*Don et al.,* *2007* ; *Ramdharry et al., 2009*). Previous studies have investigated resistance training of the knee extensor and flexor muscles, but not the hip muscles (*Lindeman et al., 1995; Chetlin et al., 2004*). The American College of Sport’s Medicine (ACSM) produce exercise prescription recommendations for resistance training, including some special populations, but this does not include people with neuropathy (*ACSM, 2009*).

This pilot study had two aims: (1) ascertain whether the hip flexor muscles could be strengthened using a home based resistance training prescription for strength and endurance, according to the general ACSM guidelines; and (2) ascertain whether training the hip flexor muscles improves the gait parameters of speed and endurance, in view of the role of the hip flexors in compensatory gait patterns.

We used a randomised, controlled, single-blinded crossover design of two 16 week blocks, either control or training periods, separated by an 8 week washout phase. Block randomisation was used to allocate the individual to group A (training first) or B (control period first), stratified using the

Charcot Marie Tooth Neuropathy Examination Score (CMTNS) (mild: 0 to 8, moderate: 9 to 16, or severe: > 16) (*Shy, et al., 2005).*

***Training protocol:*** The training protocol was informed by the American College of Sports Medicine (ACSM) guidelines on exercise prescription to increase muscle strength and endurance (*ACSM, 2009*). We used ankle weights with 0.5kg increments and progressed from loads at 40% of the maximal voluntary isometric contraction (MVC) to 60% over the training period. Subjects performed two consecutive sets of 8-12 repetitions on four training days each week for 16 weeks (*ACSM, 2009*). The exercise was performed in supine and participants moved the load from 10˚ hip extension to 45˚ hip flexion, the range observed during walking (*Don et al., 2007, Newman et al., 2007*).

We monitored participants by an exercise diary, weekly telephone calls and monthly visits to progress resistance. After the training or control period, subjects had an 8 week wash out, reversal period.

***Outcome measurement:***Subjects attended four measurement sessions: baseline, after training, after washout and after control period*.* Baseline measures of disease severity (CMTNS), lower limb muscles strength (hand held myometry) and sensory impairment (light touch and vibration threshold) were taken to characterise the participants *(Shy et al., 2007; Phillips et al., 2000; Chong and Cros, 2004)*.

The primary outcome measure was peak muscle strength. A fixed myometry set up was used to measure maximum voluntary contraction (MVC) of the hip flexors (*Schwid et al., 1999)* at 0˚, 20˚, 45˚ and 90˚ of flexion. Secondary outcome measures included the six minute walk test; the modified Physiological Cost Index *(Stockley, 2009)*; Borg perceived exertion scale during walking *(Borg, 1970)*; gait speed over 10 metres *(Pearson et al., 2004)*; perception of walking ability using the Walk-12 scale *(Graham and Hughes, 2006a)*; the Fatigue Severity Scale (FSS) *(Krupp, 1989)*; the Overall Neuropathy Limitations Scale (ONLS) *(Graham and Hughes, 2006b)*; physical activity levels using the Phone-FITT scale *(Gil et al., 2008)*.

***Analysis:***The trial was planned to detect an effect size of 17.6 Nm (1.02\*17.3) *(Lindeman et al., 1995).* The required sample size for the crossover trial for a planned standardised effect of 1.02 is 11-14 subjects (6 to 7 subjects for each treatment sequence). To allow for at least 50% dropout we aimed to recruit 32 subjects. A comparison of the multiple baselines investigated whether there had been sufficient reversal following the eight week “washout” period. We used the method of Kenward and Roger and treated the data as four repeated measures, identified by whether they are pre- or post-treatment, the treatment and the period (*Kenward and Rogers,* 2010). Based on this, a mixed effects model was used for analysis of the primary outcome measure. Secondary outcome measures were analysed using a repeated measures analysis of variance for continuous data and the Kruskal-Wallis test for ordinal data. An intention to treat analysis approach was used with the last available measurement taken forward into the analysis. As a supplementary analysis, Pearson’s correlation was used to investigate factors relating to the training effect.

Thirty two people with CMT were recruited to the study. Eighteen subjects were randomly allocated to group A and 14 to group B. No significant demographic or functional differences were seen between the two groups (Table 1). Six subjects withdrew from the study for reasons unrelated to the study intervention. Mean exercise adherence was 93%.

***Effect of training:*** No significant difference was observed in the baseline comparison so the data from group A and B were analysed together for treatment and period effects.

The mixed effects model showed increase in strength of the left hip flexors (left hip MVC: mean difference with training 0.05 ±0.14 Nm/Kg, mean difference control -0.09 ±0.40 Nm/Kg, p=0.041, 95% CI: 0.002 to 0.093) but not the right (right hip MVC: mean difference with training 0.04 ±0.20 Nm/Kg, mean difference control -0.11 ±0.42 Nm/Kg, p=0.19, 95% CI: -0.015 to 0.07).

No significant improvements were observed in walking endurance, gait speed or any of the other secondary measures (Table 2).

Variability was noted between subjects in their baseline measures and a significant but modest negative correlation was noted between the baseline hip flexor strength and the change in strength of the right leg (R leg: r=-0.39, p=0.039; L leg: r=-0.19, non-significant). The association was not as strong in the left leg and may be due to the wide variation in subjects.

***Study power:*** A retrospective power analysis was performed from this new data to inform larger scale training studies. The original sample size for this study was calculated on changes in muscle strength around 1.02 times the standard deviation (*Lindeman et al., 1995*), but here we have observed much smaller changes around 0.14 standard deviations and only achieved power at 0.2. To achieve power at 0.8, 190 people would need to be recruited for the cross over design.

The resistance training protocol used in this pilot study gave a modest outcome. Increased strength was observed in the left hip flexors, but not the right. The home based training protocol was well tolerated, and there were no adverse effects of training or concerns about overwork weakness in CMT *(Vinci et al., 2003)*.

Other than study power, other factors may have influenced the size of the training effect:

1. The ACSM training recommendation may not be optimal for people with CMT. Proximal muscles cannot be assumed to be normal and respond to exercise in the same way as a healthy subject, in view of evidence of chronic denervation in in those muscles *(Lewis et al., 2003).*
2. We relied on telephone monitoring and exercise diaries to ascertain adherence to the regime. There may have been over reporting.
3. The primary outcome measurement of isometric muscle strength did not resemble the through range training exercise. Measurement of isokinetic muscle strength would have been more specific to the prescribed exercise and may have detected greater improvements with training.
4. Variability was noted in the training effect with a negative correlation between baseline right hip flexor strength and the change in strength with training*.* Untrained individuals may show greater improvements with resistance training, as is observed in healthy individuals *(Deschenes and Kramer, 2002).*
5. The variability of response could also have been due to genetic heterogeneity of the sample.
6. Despite a small change in strength on the left side, there was no improvement in the functional measures of gait performance. There may be a threshold of change that will relate to functional carry over. We only observed a 6% improvement in left hip flexor strength. We previously saw a deterioration in gait performance after a 20% drop in hip flexor strength *(Ramdharry et al., 2009)*, so changes of this sort of magnitude could be required to observe changes in walking performance. In addition, training other muscles relating to gait may have needed to be included in the training schedule.

This pilot study investigated the effect of home based training to increase strength of the hip flexor muscles, and walking performance. A modest improvement in strength was seen only on the left side, and no changes were seen in walking measures. However, this study was useful as it showed that resistance training was well tolerated with no evidence of overwork weakness. In addition, it suggested that future studies of training in CMT may benefit from the development of a CMT specific training schedule, the selection of patients where possible with a specific genotype e.g. CMT1A or CMTX1 and the selection of patients with a minimum level of weakness for entry into the study.

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|  | **Group A** | | | **Group B** | | | **Overall sample** | |
| **Mean Age (years)** | 42 (±15) | | | 46 (±15) | | | 44 (±15) | |
| **Sex** | 8 male, 10 female | | | 9 male, 5 female | | | 17 male, 15 female | |
| **Type of CMT** | |  | | --- | | 12 CMT1 (11 CMT 1a) | | 5 CMT2 | | 1 CMT intermediate | | | | |  | | --- | | 5 CMT 1A | | 3 CMT 2 | | 4 CMT X | | 1 CMT intermediate | | 1 HSN-1 | | | | |  | | --- | | 17 CMT 1 (16 CMT 1A) | | 8 CMT 2 | | 4 CMT X | | 2 CMT intermediate | | 1 HSN-1 | | |
| **CMTES (median score)** | 9.5 | | | 11 | | | 10 | |
| ***Functional status (median scores):***  **ONLS**  **Walk-12**  **FSS**  **PhoneFITT FDI** | 3.5  35.5  25.5  55.4 | | | 4  39.5  39  50.4 | | | 4  38  30  53.75 | |
| ***Muscle strength (N):***  **Hip flexors**  **Hip extensors**  **Hip abductors**  **Hip adductors**  **Knee flexors**  **Knee extensors**  **Plantar flexors**  **Dorsiflexors** | **L** 180 ±58  227 ±58  130 ±45  153 ±69  138 ±68  277 ±100  255 ±151  75 ±59 | **R**  185 ±59  234 ±64  132 ±53  159 ±84  126 ±65  282 ±102  256 ±155  61 ±73 | **L**  193 ±62  235 ±69  127 ±42  134 ±48  140 ±60  306 ±108  224 ±126  85 ±73 | | **R**  203 ±66  234 ±68  130 ±41  133 ±48  136 ±61  317 ±100  247 ±133  66 ±66 | **L**  186 ±59  231 ±62  129 ±43  145 ±60  139 ±64  290 ±103  242 ±140  69 ±65 | | **R**  193 ±62  234 ±64  131 ±48  147 ±70  130 ±63  297 ±101  252 ±143  76 ±69 |
| ***Sensation (mean L and R):***  **Light touch**  **Vibration appearance threshold**   * **Malleolus** * **Toe** | 3.2 ±3.3  8.6 ±6.8  12.7 ±7.4 | | | 3.9 ±2.9  11.0 ±8.9  12.5 ±9.6 | | | 3.6 ±3.2  9.6 ±7.8  12.6 ±8.3 | |

**Table 1:** Baseline characteristics of study participants at allocation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Pre training** | **Post training** | **Pre control** | **Post control** |
| **Hip flexor MVC averaged across angles (Nm/kg): left hip** | **1.14 ±0.44\*** | **1.19 ±0.45\*** | **1.13 ±0.41\*** | **1.11 ±0.47\*** |
| **Hip flexor MVC averaged across angles (Nm/kg): right hip** | **1.17 ±0.45** | **1.21 ±0.43** | **1.17 ±0.43** | **1.12 ±0.47** |
| **6 minute timed walk (m)** | **342 ±-67** | **350 ±-68** | **352 ±-73** | **347 ±-75** |
| **Walking speed (self selected) (m/s)** | **1.18 ±0.24** | **1.19 ±0.24** | **1.18 ±0.21** | **1.19 ±0.23** |
| **Walking speed (maximum) (m/s)** | **1.48 ±0.33** | **1.47 ±0.36** | **1.48 ±0.32** | **1.44 ±0.32** |
| **CMTES (median)** | **10.5** | **11** | **10** | **12** |
| **Walk 12 (median)** | **34** | **33** | **36.5** | **36** |
| **FSS (median)** | **29.5** | **27** | **29** | **31** |
| **Borg (median)** | **11** | **11** | **12** | **12** |
| **Modified PCI (beats/min/m)** | **1.93 ±0.59** | **1.89 ±0.59** | **1.89 ±0.51** | **1.96 ±0.57** |
| **Phone FITT FDI (median)** | **55.4** | **45.7** | **49.4** | **48.5** |

**Table 2:** Summary of outcome measures. Mean ± standard deviation unless stated otherwise. \* p<0.05

**References**

American College of Sports Medicine (2009). ACSM’s Guidelines for Exercise Testing and Prescription 8th edition, Lippincott Williams and Wilkins, Baltimore.

Borg B (1970). Psychophysical basis of perceived exertion. Medicine and Science in Sports and Exercise 14: 377–381.

Chetlin RD, Gutmann L, Tarnopolsky M, Ullrich IH, and Yeater RA (2004). Resistance training effectiveness in patients with Charcot-Marie-Tooth disease: recommendations for exercise prescription. Arch Phys Med Rehabil 85:1217–1223.

Chong PST, Cros DP (2004). Technology literature review: quantitative sensory testing. Muscle Nerve 29: 734–747.

Deschenes MR and Kraemer WJ (2002). Performance and physiologic adaptations to resistance training. Am J Phys Med Rehabil 81: S3–16.

Don R, Serrao M, Vinci P, Ranavolo A, Cacchio A, Ioppolo F, Paoloni M, Procaccianti R, Frascarelli F, De Santis F, Pierelli F, Frascarelli M, and Santilli V (2007). Foot drop and plantar flexion failure determine different gait strategies in Charcot-Marie-Tooth patients. *Clin Biomech* 22: 905–916.

Graham RC , Hughes RAC (2006). A modified peripheral neuropathy scale: the Overall Neuropathy Limitations Scale. J. Neurol. Neurosurg. Psychiatr 77: 973–976.

Graham RC, Hughes RAC (2006). Clinimetric properties of a walking scale in peripheral neuropathy. J Neurol Neurosurg Psychiatr 77: 977–979.

Kenward M, Roger J (2010). The use of baseline covariates in crossover studies. Biostatistics 11: 1–17.

Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD (1989). The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Archives of Neurology 46: 1121–1123.

Lewis RA, Li J, Fuerst DR, Shy ME, Krajewski K (2003). Motor unit number estimate of distal and proximal muscles in Charcot-Marie-Tooth disease. Muscle Nerve 28: 161-167.

Lindeman E, Leffers P, Spaans F, Drukker J, Reulen J, Kerckhoffs M, Köke A (1995). Strength training in patients with myotonic dystrophy and hereditary motor and sensory neuropathy: a randomized clinical trial. Arch Phys Med Rehabil 76: 612–620.

Newman CJ, Walsh M, O’Sullivan R, Jenkinson A, Bennett D, Lynch B, and O’Brien T (2007). The characteristics of gait in Charcot-Marie-Tooth disease types I and II. Gait Posture 26: 120–127.

Pearson OR, Busse ME, van Deursen RWM, Wiles CM (2004). Quantification of walking mobility in neurological disorders. QJMed 97: 463–475.

Phillips BA, Lo SK, and Mastaglia FL (2000). Muscle force measured using “break” testing with a hand-held myometer in normal subjects aged 20 to 69 years. Arch Phys Med Rehabil 81: 653–661.

Ramdharry GM, Day BL, Reilly MM, and Marsden JF (2009). Hip flexor fatigue limits walking in Charcot-Marie-Tooth disease. Muscle Nerve 40: 103–111.

Schwid SR, Thornton CA, Pandya S, Manzur KL, Sanjak M, Petrie MD, McDermott MP, Goodman AD (1999). Quantitative assessment of motor fatigue and strength in MS. Neurology 53: 743–750.

Shy ME, Blake J, Krajewski K, Fuerst DR, Laura M, Hahn AF, Li J, Lewis RA,

Reilly M (2005). Reliability and validity of the CMT neuropathy score as a measure of disability. Neurology 64:1209-1214.

Stockley R (2009). A new measure of the energy cost of walking in people with peripheral neuropathy: the modified physiological cost index. Chartered Society of Physiotherapy Congress, Liverpool, UK, 2009.

Vinci P, Esposito C, Perelli SL, Antenor JAV, Thomas FP (2003). Overwork weakness in Charcot-Marie-Tooth disease. Arch Phys Med Rehabil 84: 825–827.