



Safety and efficacy of progressive resistance exercise for Charcot-Marie-Tooth disease in children: a randomised, double-blind, sham-controlled trial

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Summary

Background Exercise is potentially therapeutic for neuromuscular disorders, but a risk of harm exists due to overwork weakness. We aimed to assess the safety and efficacy of progressive resistance exercise for foot dorsiflexion weakness in children with Charcot-Marie-Tooth disease.

Methods We did this randomised, double-blind, sham-controlled trial across the Sydney Children's Hospitals Network (NSW, Australia). Children aged 6–17 years with Charcot-Marie-Tooth disease were eligible if they had foot dorsiflexion weakness (negative Z score based on age-matched and sex-matched normative reference values). We randomly allocated (1:1) children, with random block sizes of 4, 6, and 8 and stratification by age, to receive 6 months (three times per week on non-consecutive days; 72 sessions in total) of progressive resistance training (from 50% to 70% of the most recent one repetition maximum) or sham training (negligible non-progressed intensity), using an adjustable exercise cuff to exercise the dorsiflexors of each foot. The primary efficacy outcome was the between-group difference in dorsiflexion strength assessed by hand-held dynamometry (expressed as a Z score) from baseline to months 6, 12, and 24. The primary safety outcome was the between-group difference in muscle and intramuscular fat volume of the anterior compartment of the lower leg assessed by MRI (expressed as a scaled volume) from baseline to 6 months and 24 months. Participants, parents, outcome evaluators, and investigators other than the treatment team were masked to treatment assignment. Analysis was by intention to treat. The trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12613000552785.

Findings From Sept 2, 2013, to Dec 11, 2014, we randomly assigned 60 children to receive progressive resistance exercise (n=30) or sham training (n=30), and 55 (92%) children completed the trial. ANCOVA-adjusted Z score differences in dorsiflexion strength between groups were 0 (95% CI -0.37 to 0.42; p=0.91) at 6 months, 0.3 (-0.23 to 0.81; p=0.27) at 12 months, and 0.6 (95% CI 0.03 to 1.12; p=0.041) at 24 months. Scaled muscle and fat volume was comparable between groups at 6 months (ANCOVA-adjusted muscle volume difference 0, 95% CI -0.03 to 0.10, p=0.24; and fat volume difference 0, 95% CI -0.01 to 0.05, p=0.25) and 24 months (0, -0.08 to 0.12, p=0.67; and 0, -0.05 to 0.03, p=0.58). No serious adverse events were reported.

Interpretation 6 months of targeted progressive resistance exercise attenuated long-term progression of dorsiflexion weakness without detrimental effect on muscle morphology or other signs of overwork weakness in paediatric patients with Charcot-Marie-Tooth disease.

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Introduction

Charcot-Marie-Tooth disease describes a group of inherited peripheral neuropathies that are among the most common neurological disorders. It affects both sexes and all backgrounds. Mutations in more than 80 genes have been implicated, with most patients exhibiting a typical phenotype characterised by onset in the first or second decade of life and slow lifelong disease progression. Among a myriad of motor and sensory impairments, muscle weakness, due to loss of or damage to large-calibre motor axons,¹ is the most debilitating problem for patients. Weakness is length dependent, and consequently distal foot muscles responsible for dorsiflexion are among the most affected. The weakness of these muscles causes physiological and functional

changes, leading to painful foot deformities (such as pes cavus and hammer toes), lifelong difficulty performing everyday tasks (such as walking and climbing stairs), and injuries resulting from trips and falls.² In a survey³ of 407 adults with Charcot-Marie-Tooth disease, 406 (99.7%) complained of foot weakness and reported that it had the greatest impact on their quality of life.

Despite rapid advances in molecular genetics in the past decade, no effective treatment is available for patients with Charcot-Marie-Tooth disease, although results of animal studies and early-phase clinical trials have helped to identify promising drug candidates.^{4,5} Physical therapies such as exercise, with immediate and potentially universal application, are commonly used, yet little is known about their efficacy and safety. In healthy

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Research in context

Evidence before this study

We did a systematic review by searching MEDLINE, Allied and Complementary Medicine Database, CINAHL, Cochrane Library, Embase, Scopus, SPORTDiscus, and Web of Science for relevant articles published until Feb 14, 2015. We used keywords related to “Charcot-Marie-Tooth*” AND “Exercise\$*” in our search strategy. Studies in any language of any design including participants of any age with confirmed diagnosis of Charcot-Marie-Tooth disease that investigated the effects of exercise were eligible for inclusion. We identified 11 articles including nine unique studies (eight adult studies and our FAST pilot study). Methodological quality (using a modified Downs and Black checklist) was moderate, sample sizes were small (1–32), and interventions (five progressive resistance exercise, two cycling, and two combination programmes) and outcome measures (muscle strength, function, physiology, and safety) varied widely, which precluded pooling for meta-analysis. Of the few studies that investigated progressive resistance exercise in Charcot-Marie-Tooth disease, training typically involved the less affected proximal muscles, trials were limited to adults, and variable short-term responses in strength and function were observed.

Added value of this study

To our knowledge, this study is the first randomised trial to assess progressive resistance exercise for children with Charcot-Marie-Tooth disease. We found that targeted short-term moderate-intensity progressive resistance exercise of the foot dorsiflexors, when using an adjustable exercise cuff, could attenuate long-term progression of dorsiflexion weakness without detrimental effect on muscle morphology or other signs of overwork weakness.

Implications of all the available evidence

The moderate-intensity progressive resistance exercise of the foot dorsiflexors in our trial represents the first effective therapy for paediatric patients with Charcot-Marie-Tooth disease. Considering that muscle weakness, due to loss of or damage to large-calibre motor axons, is the most debilitating problem for patients with this disease, access to physical therapies such as exercise might slow progression of muscle weakness and associated functional changes that lead to painful foot deformities, difficulty performing everyday tasks, and injuries resulting from trips and falls.

individuals, progressive resistance exercise promotes neural adaptations, skeletal muscle hypertrophy, and strength gains.^{6–8} However, for Charcot-Marie-Tooth disease, although it is the weakness of the distal muscles that leads to the most disabling sequelae, very little is known about the effect of progressive resistance training.⁹ Of the few studies^{10–12} that have investigated strength training for patients with this disease, training typically involved the less affected proximal muscles, trials were limited to adults, and variable short-term responses in strength and function were observed. Evidence regarding training of the dorsiflexion muscle group is limited to a paediatric case study,¹³ which found that a home-based, moderate-intensity, progressive resistance programme increased strength and function.

The possibility that progressive resistance exercise might cause long-term overwork weakness and more rapid disease progression in patients with neuromuscular disorders is of concern. These concerns stem from early research of overworking denervated skeletal muscle in post-polio syndrome, especially without medical supervision.^{14,15} Additionally, patients who have neuromuscular disorders with altered muscle pathology, particularly those with abnormalities of muscle fibre membrane proteins such as the muscular dystrophies, are hypothesised to be at increased risk of exercise-induced injury from high-intensity resistance exercise because of the inability to adequately repair injured muscle.¹⁶ This risk is less relevant in a primary neuropathy such as Charcot-Marie-Tooth disease.

We aimed to assess the long-term safety and efficacy of progressive resistance exercise for foot dorsiflexion weakness in children with Charcot-Marie-Tooth disease. Because of the progressive nature and underlying pathophysiology of the disease, intervention during childhood was expected to have the greatest likelihood of success because axonal degeneration is mild at disease onset and the capacity for functional recovery deteriorates through later life.¹⁷

Methods

Study design and participants

This randomised, double-blind, sham-controlled trial was designed and undertaken by investigators at The University of Sydney and Sydney Children’s Hospitals Network (Randwick and Westmead, NSW, Australia). The FAST study protocol¹⁸ was approved and monitored by the Sydney Children’s Hospitals Network Human Research Ethics Committee (HREC/13/SCHN/21).

We enrolled children aged 6–17 years with Charcot-Marie-Tooth disease, diagnosed by a paediatric neurologist specialising in inherited peripheral neuropathies, on the basis of eligibility criteria that have been described previously.¹⁸ Briefly, affected children with foot dorsiflexion weakness (defined by a negative Z score based on age-matched and sex-matched normative reference values¹⁹) and ability to adhere to the protocol were eligible for inclusion. Parents or caregivers provided written informed consent and, when appropriate, child assent was obtained.

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