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Charcot-Marie-Tooth

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University of North Dakota

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CHARCOT-MARIE-TOOTH

by

Josh Anderson
University of North Dakota
Doctor of Physical Therapy, 2015

A Scholarly Project Submitted to the Graduate Faculty of the

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in partial fulfillment of the requirements for the degree of

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This Scholarly Project, submitted by Josh Anderson in partial fulfillment of the requirements for the Degree of Doctor of Physical Therapy from the University of North Dakota, has been read by the Advisor and Chairperson of Physical Therapy under whom the work has been done and is hereby approved.

(Graduate School Advisor)

(Chairperson, Physical Therapy)
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Title                       Charcot-Marie- Tooth

Department                 Physical Therapy

Degree                     Doctor of Physical Therapy

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I would like to thank my parents, Dave and Pam, for their unconditional love and support when I decided to go back to school for Physical Therapy. It has been a long journey but will be worth it in the end.
ABSTRACT

Background and Purpose: Charcot-Marie-Tooth (CMT) is the most common inherited peripheral neuropathy and affects both motor and sensory nerves. Clinical presentation is similar among all types and results in distal muscle atrophy and weakness, diminished sensation and proprioception, and balance and gait disturbances. Pes cavus is a prominent feature. Although gene therapy and neurotrophic growth factors show promise as treatment, physical therapy remains the most viable option at this time. The purpose of this case report is to determine the effect that physical therapy may have on both physical and psychological outcomes related to CMT.

Case Description: Patient was a 51-year-old-female presenting to physical therapy with a diagnosis of CMT. She presented with lower extremity pain, muscle weakness and atrophy, diminished or absent sensation and proprioception, gait deviations, and increased difficulty navigating stairs. Her main goal was to remain an independent ambulator for as long as possible. Her pain was managed with gabapentin. She did not report any involvement with her upper extremities.

Intervention: A resistance training program focusing on balance, stepping activities and lower extremity strength was initiated carried out as an outpatient and home exercise program. Massage and soft tissue work was applied to the legs and feet.

Outcome: The patient was seen for 18 total visits. At discharge, her balance, tandem stance, lower extremity strength all improved. She reported feeling more confident with
ambulation and was less anxious about the disease process. A referral to a podiatrist was given for custom orthotics.

*Discussion:* Patient's with CMT often report difficulty with mobility and ambulation, specific activity impairments, fatigue, and emotional distress. In spite of this, they are often not referred to or attend physical therapy as the perceived benefit is small.
CHAPTER I
BACKGROUND AND PURPOSE

Charcot-Marie-Tooth (CMT) is the most commonly inherited peripheral neuropathy. It is named after the three physicians who first described it: Jean-Martin Charcot, Pierre Marie, and Howard Henry Tooth. CMT is also known as peroneal muscular atrophy (PMA) or hereditary motor sensory neuropathy (HMSN). CMT is found world-wide among all races and ethnic groups and affects an estimated 40 individuals in every 100,000.¹ There are many forms of CMT disease, including CMT1, CMT2, CMT3, CMT4 and CMTX. For an overview of the genotypes, phenotypes and clinical presentations, the reader is referred to the work of El-Abassi et al.² CMT1 accounts for more than two-thirds of all cases. CMT is not contagious and not attributable to an environmental cause.

Some types of CMT cause damage to the myelin sheaths (CMT1: typically inherited in an autosomal dominant pattern; CMT4: inherited in an autosomal recessive pattern) while some types damage the nerve axons themselves (CMT2: inherited in an autosomal dominant pattern).² Both the sensory and/or the motor fibers can be affected causing weakness, numbness, and diminished or complete loss of sensation most commonly in the distal extremities but any nerve of the body can become affected. In most cases, it is a slowly progressing peripheral neuropathy. Any signs of a quickly deteriorating neurological process should prompt an immediate re-evaluation as this can
indicate a much more serious or life threatening disease process. CMT in itself is generally not considered life threatening but rare variants of the disease can affect the autonomic respiratory and cardiac nerve fibers, compromising heart and lung function.\textsuperscript{3} Brain function is normally spared.

Individuals with CMT1 or CMT2 usually become symptomatic between age 5 and 25 years with age of onset ranging from infancy to the fourth and subsequent decades. Clinical severity is variable, ranging from extremely mild disease that goes unrecognized by the affected individual and physician to considerable weakness and disability.\textsuperscript{1} Although there are many different genetic causes of CMT, all types tend to have remarkably similar symptoms. Pes cavus is usually present, although pes planus can also be typical. As the disease progresses, structural deformities take place depending on which nerves and corresponding muscles are affected, causing abnormal forces across the joint. Typically, the distal nerves of the feet and hands are affected first.\textsuperscript{2} Proximal muscle weakness is rarely present except in the most severely affected patients. Although it is not fully understood why proximal muscles are typically spared, the mutations in many different genes lead to dysfunction of many proteins eventually leading to axonal degeneration that is length-dependent.\textsuperscript{4,5} Muscle atrophy of the lower legs and intrinsic foot and hand musculature is also common. Muscle atrophy in the lower leg can lead to what has been described as an “inverted champagne bottle” appearance. Neuropathic pain such as numbness and tingling can range from annoying pain to more debilitating pain that can affect activities of daily living and typically requires medication to manage.\textsuperscript{6}

CMT is typically diagnosed by a neurologist through a thorough neurological evaluation, including a complete family history, physical exam, and nerve conduction
tests. If appropriate, genetic testing can confirm the diagnosis. For a diagnosis of CMT1, a reduced ulnar nerve conduction velocity of less than 38 m/sec is required. In comparison, normal ulnar nerve conduction velocities average 52.4 m/s for adults aged 50-59 years old. Typically, the first signs may include leg weakness, unexplained frequent tripping, and/or falling. A physical exam may show (1) foot drop, (2) reduced or absent deep tendon reflexes, (3) atrophy in the feet and lower leg resulting in an inverted champagne bottle appearance (4) high arches, (5) hammer toes, (6) problems with balance, and (7) gait disturbances. Patients may lose feeling in their hands and/or feet, putting them at risk for blisters, burns, and sores.

There is no known cure for CMT. Large randomized controlled studies have examined the efficacy of ascorbic acid, a vital component for the regeneration of nerves. Rat models have shown promise, but these studies have not shown any beneficial effects for humans with CMT. Other investigational therapies underway include identifying neurotrophic growth factors, specifically neurotrophin 3 (NT3), which expressed by Schwann cells to promote myelination. Many gene therapy investigations are also underway. Certain medications, such as vinca alkaloids (vincristine) pose a definite risk and can exacerbate CMT symptoms. Gabapentin is believed to have a negligible or doubtful risk of exacerbating CMT symptoms.

Moderate resistance training has been shown to be effective at reducing fatigue and increasing quality of life in people with CMT. Although an exact resistance has not been established, it is generally thought that too high of a resistance performed too often can be deleterious to people with CMT and cause overuse weakness. However, more recent evidence refutes this theory. A home-based strength training program for the
knee extensors and flexors and elbow extensors and flexors, progressively increasing resistance through 4 phases over 12 weeks, resulted in improved strength and activities of daily living and was equally effective for men and women with CMT. The additional ingestion of creatine has not been found to be beneficial. A 12-week exercise program of moderate resistance (30% of maximum isometric force) resulted in strength gains ranging from 4% to 20% without any notable harmful effects. However, in the same population, a 12-week high resistance exercise program (ie, training at the maximum weight a subject could lift 12 times) showed no added beneficial effect compared with the moderate-resistance program and evidence showed overwork weakness in some of the subjects. Lindeman et al show that progressive resistance training can increase muscle force production as measured through surface EMG. A 12-week walking program consisting of 30 minutes per day, 3 to 4 times per week reduced both submaximal heart rate and blood pressure and was well tolerated by all individuals. Twenty-four weeks of interval training exercise cycling has also shown to increase cardiorespiratory function in people with CMT. Physical therapy, occupational therapy, and moderate physical activity continue to be the mainstay of treatment and can be beneficial in reducing fatigue, while increasing endurance and strength.

The purpose of this case report is to describe the anatomical and physiological effects CMT has on the body, patient presentation at initial evaluation, the effects of a strength and conditioning program, and describe the patient's functional status and her perception of the disease process following care.
CHAPTER II

CASE DESCRIPTION

Examination

History

This patient was a 51-year-old female presenting to physical therapy with a diagnosis of Charcot-Marie-Tooth. She was diagnosed in early 2005 with the disorder but was unsure of the type. The patient had a family history of CMT as both her mother and grandmother had the disease. At the time of diagnosis, she was independent in all activities but did report stubbing her toes often and falling at various times. Before she was diagnosed, she attributed these falls to clumsiness. She had recently started having more trouble negotiating stairs, especially if she was holding anything with her arms such as laundry and now required use of handrails. She also stated that she had trouble descending hills or sidewalks but does not have as much trouble ascending them. She reports feeling stronger leading with her left leg up stairs.

After she was diagnosed in 2005, she was told that not much could be done for her. She was referred to a specialist at a local University hospital where she was again referred to an orthopedic surgeon for surgery to correct her foot deformity. She refused surgery at that time but was prescribed gabapentin to reduce the nerve pain in her feet. Since then, she has seen various healthcare practitioners who have tried various
treatments, including acupuncture and massage, without much success at relieving pain and/or improving function.

She currently works an office job and sits at a desk for upwards of ten hours per day taking only occasional standing breaks. She attributed the prolonged sitting to fear of walking and possibly tripping or falling in the workplace. She lives in a two-story house with her husband and has two children, who are both in college. She reported being previously independent in all activities of daily living (ADLs) but currently has trouble negotiating stairs and hills. She was eventually referred to physical therapy with orders to evaluate and design an appropriate strength and conditioning program. She stated that she is knowledgeable about CMT and its course but was frustrated that she has been “bounced” around from practitioner to practitioner without anyone really trying anything. She was also anxious about the course of the disease due to her mother and grandmother ending up in wheelchairs from CMT. Because of this, she was highly motivated to try physical therapy. She denied any history of alcohol or tobacco use.

Pain

Her pain is managed by gabapentin which she takes three times a day: in the morning, midafternoon, and before bed. The mechanism by which gabapentin exerts its analgesic action is unknown but is currently prescribed for neuropathic pain. Gabapentin is a gamma-aminobutyric acid analog (GABA), which is the chief inhibitory neurotransmitter in the human nervous system. However, gabapentin is not appreciably metabolized in humans but rather acts to increase GABA synthesis thus inhibiting the nervous system and signal transmission leading to reduced pain sensation. Gabapentin typically keeps her pain manageable, which she rated at 3/10 with 0 being no pain and 10.
being the worst imaginable pain. Her pain never decreases to 0 and will get as bad as a
7/10 if she misses a gabapentin dosage. Due to the foot and leg pain, she often has
difficulty falling asleep at night. She has found that quickly performing sidelying hip
abduction at very high repetitions (upwards of 125 on left, often not as many on the right
as that side does not feel as strong) fatigues her and she will fall asleep.

Objective tests and measures

Observation revealed genu valgum, genu recurvatum, pronated feet (left greater
than the right), slight atrophy throughout bilateral leg musculature, most notably in the
fibularis and triceps surae. She does not currently wear any braces or ankle-foot orthoses
(AFO) but does wear over-the-counter foot orthotics. At this time, she does not believe
she needs a custom foot orthotic or an AFO. The bony prominences were readily seen
throughout her feet bilaterally due to the atrophy of her lower leg and intrinsic foot
muscle. No skin breakdown or pressure sores are readily apparent on her feet and ankles.

An observational gait analysis revealed limited heel strike and flat foot which
slaps down (possibly because she lacks sensation and/or proprioception in her feet and
has general DF weakness) at initial contact. During mid-stance, her adductors pull her
into a slight “scissoring-type” gait. She displayed minimal push-off during late stance
phase which would cause her knee to hyperextend and lock out. During swing phase, she
displayed a slight circumduction swing through to increase her foot clearance. She does
not use an assistive device.

Her lower extremity range of motion was within normal limits bilaterally except
for reduced dorsiflexion bilaterally. Joint play assessment revealed bilateral
hypermobility throughout her feet. Her lower extremity strength graded 3+/5 to 4/5
bilaterally throughout except for left hip abduction graded 5-/5. Pin prick and light touch (gently sweeping the hands over the legs and feet) sensation were diminished or absent throughout bilateral legs and feet. She stated that she has been told that she has over 90% sensory loss in her feet and that she had mild hypersensitivities to hot and cold temperatures. Patellar and Achilles reflexes were diminished bilaterally. Single-leg stance required continuous fingertip touch for balance. She was unable to perform a full squat due to her hip joints internally rotating and adducting causing genu valgum. Upper extremity testing was deferred due to no involvement at this time. A McGill pain questionnaire was filled out but neither a functional scale such as a SF-36 nor a more specific scale such as the CMT neuropathy score was administered.

**Evaluation**

The patient is a 51 year old female presenting to physical therapy with a diagnosis of CMT. Her chief complaint was anxiousness related to the disease process and potentially ending up in a wheelchair which happened to both her mother and grandmother. She remains independent in all activities with the exception of navigating stairs which she requires the use of a hand rail. Because of this, she is unable to carry anything (ie, laundry) up and down the stairs in her house. Her pain remains at a 2 to 3 out of 10 and is managed by gabapentin, which she takes daily. An observational gait analysis revealed slight foot slap and knee hyperextension at initial contact, reduced push-off during late stance, and a circumduction swing through gait to compensate for her slight foot drop. Single-leg balance requires continuous finger-tip touch assistance. Sensation is diminished or absent throughout her legs bilaterally and she displays mild
hypersensitivities to hot and cold. Muscle atrophy is present throughout her legs and feet. Her upper extremities remain unaffected at this point.

PT Diagnosis

According to the Guide to Physical Therapist practice, the patient was classified under the preferred practice pattern 5F: Impaired Peripheral Nerve Integrity and Muscle Performance Associated with Peripheral Nerve Injury. An ICD-9-CM code of 356.1: Peroneal muscular atrophy was used to classify the disease.

Prognosis

Prognosis was judged to be fair to good due to the progressive nature of the disease and lack of viable treatment options. However, due to high motivation levels and having overall good health, and the fact that she was able to maintain an almost normal grade (5-/5) in side-lying hip abduction by performing high repetitions almost nightly to aid her in falling asleep, it was hypothesized that with a well-rounded strength and conditioning program she may be able to offset some of the negative effects, such as deconditioning due to reduced physical activity, of the disease process.

The primary long term goal for the patient was to remain an independent ambulator for as long as possible and to potentially offset the deconditioning associated with reduced activity levels due to CMT. Other long term goals included decreased pain levels if she happened to miss a gabapentin dosage, maintaining current manual muscle test scores or possibly increasing them to 4/5 throughout bilateral lower extremity, improved stepping and gait performance to better negotiate stairs, and reduce the risk of future falls. Short term goals included improving her single leg balance with eyes open to
20 seconds bilaterally and being 100% adherent with her home exercise program. These goals were deemed to be realistic and attainable by both the patient and therapist.
CHAPTER III
INTERVENTION

A comprehensive resistance training program was developed and was carried out in an outpatient clinic and as a home exercise program. The main focus of the program was on the lower extremity although upper extremity exercises were also incorporated. An emphasis was placed on balance and stepping activities to help prevent future falls and negotiation of stairs and hills. Manual therapy in the form of soft tissue massage was performed to her lower legs and feet as the patient reported relief with this technique. Due to her lack of sensation to her feet and legs, she was encouraged to check them daily for skin breakdown. The following table contains a list of interventions and exercises performed.

<table>
<thead>
<tr>
<th>Table 1. Interventions and Exercises Performed</th>
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</thead>
<tbody>
<tr>
<td><strong>Lower Extremity</strong></td>
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<tr>
<td>-Manual therapy including soft tissue massage to feet and lower leg</td>
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<tr>
<td>-Doorway squats</td>
</tr>
<tr>
<td>-Single leg balance/tandem walking</td>
</tr>
<tr>
<td>-Heel/toe raises</td>
</tr>
<tr>
<td>-Vigor Gym Squats</td>
</tr>
<tr>
<td>-Multi-planar lunges</td>
</tr>
<tr>
<td>-Step-ups (forward and lateral)</td>
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<tr>
<td>-Walking lunges</td>
</tr>
</tbody>
</table>

A typical treatment session would include 10 to 15 minutes of soft tissue work to her feet and lower legs and 45 minutes of resistance training exercise. She would perform 6 to 8 exercises in any given session and exercises would be alternated from session to
session. Progressions included higher steps, more repetitions, quicker repetitions, and removal of any external assistance, ie, fingertip touch during SL stance.

Although stationary cycling would be an appropriate exercise type, she did not have one at home and was not a member of a health club so that she could have access to one. Outdoor cycling was not appropriate for her due to balance deficits and that a few years ago, she noticed that her right foot would slip off of the pedal at random times. She was not sure why this would happen but the therapist speculated that it may be due to lack of proprioception in her feet. Treadmills were also deemed inappropriate due to her foot drop, lack of proprioception and increased risk of a fall potentially leading to injury. Swimming was suggested but due to time constraints and lack of proximity to a pool she stated that swimming was not a realistic option at this point.
CHAPTER IV
OUTCOMES

The patient was seen for eighteen total visits over a twenty week span at which point a mutual decision was made to discharge her. A referral to a podiatrist was given should she decide to have custom orthotics made. Her home exercise program was progressed each session by increasing the number of reps, weight, sets, or amount of support for balance. She reported 100% adherence with no increases in fatigue or soreness and stated that she would often perform 2-3 times as many repetitions as the program called for. Lower extremity manual muscle testing increased from 3+/5 to 4/5 bilaterally throughout. Single leg balance for thirty seconds improved from continuous to intermittent fingertip touch. Tandem stance improved from requiring intermittent fingertip touch to independent tandem stance with external perturbations. She reported feeling more confident with ambulation and would take more walking breaks during work. She continued to be diligent with foot checks for skin breakdown that could result in a neuropathic ulcer. No apparent skin breakdown was evident at any point during therapy. She was versed in proper footwear and areas that are more prone to skin breakdown such as bony prominences and metatarsal heads. Overall, she stated that her pain may be somewhat better but will still increase to a 6-7/10 if she misses a gabapentin dosage. At her fourth session of therapy, she did report falling while shopping for groceries but said this was due to her being in a rush.
CHAPTER V
DISCUSSION

CMT is a slowly progressing peripheral neuropathy that affects both sensory and motor nerves in a variety of ways (demyelination, axonal destruction, etc) depending on the genotype. Patients frequently report difficulty with mobility and ambulation, specific activity impairments, and emotional distress closely followed by pain, numbness and fatigue.\textsuperscript{24} Health-related quality of life (HRQoL) in CMT was strongly predicted by lower limb weakness and to a lesser extent by leg cramps, suggesting clinical trials targeting weakness and cramps may improve HRQoL in patients with CMT.\textsuperscript{25} A survey by Calvert et al showed that people with rare neurological disorders, such as CMT, are less likely to seek out healthcare and/or social services that could have a positive impact on the HRQoL and may reflect a lack of coordination of care.\textsuperscript{26} A lack of effective interventions may be contributing to this and as such, healthcare practitioners that encounter these types of patients are less likely to refer them for treatment such as physical or occupational therapy. Patients often perceive physical and mental benefits from rehabilitation, but also perceive that the best rehabilitation program is not being performed. On top of that, familiar and/or caregivers do not necessarily think the rehabilitation is effective which may be due to the small benefits generally achieved by the patient and not readily appreciated by the family or caregiver.\textsuperscript{27} While the research is somewhat conflicting and sparse as to the effectiveness of physical therapy at improving
function in people with CMT, it is currently the best available option until other therapies such as gene or neurotrophic factors (ie, NT3) become viable.

Surgery is often offered to patients with CMT to correct structural deformities of their feet to increase gait efficiency. At this point, she has not considered having surgery as she remains an independent ambulator. She was, however, encouraged to try a custom orthotic as opposed to the over-the-counter orthotics she currently used. Due to the flexible nature of her pes planus, the therapist speculated that a custom orthotic could help to improve gait efficiency and even possibly reduce the risk for future falls.

Reflective Practice

One of the main reasons for using CMT for this case report was the lack of familiarity with not only CMT, but also the interventions currently used to treat it. On an interesting and encouraging note, because she was able to maintain 5-/5 manual muscle grade in her left hip abduction (possibly from performing high repetition side-lying hip abduction nightly), the therapist speculated that early intervention for patients with CMT may offset the progression of the disease and potentially allow for strength gains to be made. However, due to the progressive nature of the disease and the degeneration of myelin or the axons themselves, any benefits or improvements are generally small and probably attributable to the reversal of general deconditioning rather than direct improvements to the nerves and muscles themselves.

Other things that could have been addressed were upper extremity testing such as grip strength, sensation, reflexes and proprioception. This could have allowed for some objective tests and measures to quantify any progression of the disease in the upper
extremity. Although the clinic did not have a handheld dynamometer to assess muscle strength, this could have objectively quantified any potential strength gains rather than subjective manual muscle scores. Although a McGill pain questionnaire was filled out, no specific functional scale, such as the CMT neuropathy scale or SF-36 was administered, it could have been beneficial to fill one out to assess her current quality of life, to have a better understanding of how she perceives the disease process is affecting her life, and to detect any changes in functions that therapy may have had.

Sometimes what gets lost in practice is the fact that we get so caught up in seeing or making improvements in everyone we treat, we often forget that when we are dealing with slowly progressing diseases such as CMT, the fact that they are improving as opposed to declining should be viewed in a more positive light. While we do not currently have the ability to restore myelin or regenerate axons in patients that have a slowly progressing peripheral neuropathy, physical activity may benefit people with CMT. In spite of the lack of evidence for physical therapy, we as practitioners should be even more diligent as to how we help and treat these patients. They should not be dismissed or tossed from one practitioner to another because there is no cure. At the very least, referrals should be given to the appropriate healthcare professionals as these patients can typically benefit from increased quality of life such as sleeping better, reduced pain, coping strategies and possibly increased strength and endurance. In addition to that, if a diagnosis is made early and referral to physical or occupational therapy is made, perhaps some of the deconditioning from inactivity can be staved off and muscle strength can be maintained longer or, at the very least, the deterioration can be minimized.
<table>
<thead>
<tr>
<th>Study</th>
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<th>Intervention</th>
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<th>Significant outcomes</th>
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<tr>
<td>Wright, NC et al (1996)</td>
<td>N=8, 4 men, 4 women, mean age 36.6 y/o; slowly progressing NMD</td>
<td>12-week walking</td>
<td>Resting, submax and peak HR, SBP and DBP, O2 uptake, peak power output</td>
<td>-Submax HR ↓</td>
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<td></td>
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<td>15-30min, 3-4x/week</td>
<td></td>
<td>-Submax SBP ↓</td>
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<td></td>
<td>50-60% HRR</td>
<td></td>
<td>-Well tolerated</td>
</tr>
<tr>
<td>Mhandi, LE et al (2007)</td>
<td>N=8 (all men); CMT1: mean age 32y/o; CMT2: mean age 34 y/o</td>
<td>24-week cycling program</td>
<td>VO2max, peak power, knee ext/flex strength, ascending/descending 9 stairs, walking</td>
<td>-VO2max ↑</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>-Peak power ↑</td>
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<tr>
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<td></td>
<td>-Stairs time ↓</td>
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<td></td>
<td></td>
<td>-50m walk time ↓</td>
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<td></td>
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<td></td>
<td></td>
<td>-60m walk time ↓</td>
</tr>
<tr>
<td>Lindeman, E et al (1999)</td>
<td>N=33 (myotonic dystrophy); N=29 (CMT)</td>
<td>24 week progressive RT</td>
<td>Isometric knee extension force production measured via surface EMG (maximum voluntary contraction (MVC))</td>
<td>-MVC knee extension force ↑ 21%</td>
</tr>
<tr>
<td>Chetlin, RD et al (2004)</td>
<td>N=20, 11 women, 9 men; mean age 45y/o</td>
<td>12 weeks progressive strength training, 3d/wk</td>
<td>Timed ADLs, isometric UE and LE strength, body composition</td>
<td>-Chair rise, supine rise, stair climb improved. -Women achieved 80% normal strength norms in 6/8 measurements of MVIS -Well tolerated</td>
</tr>
<tr>
<td>Chetlin, RD et al (2004)</td>
<td>N=20, 11 women, 9 men; mean age 45y/o</td>
<td>Progressive strength training 3d/wk, 12 weeks with or without creatine supplementation</td>
<td>Muscle fiber type and size, strength, and ADLs</td>
<td>-Type IIB fiber size ↑ -Lift and reach, chair rise, supine rise and stair improved significantly -No benefit from creatine</td>
</tr>
</tbody>
</table>

NMD = Neuromuscular disease; HRR = heart rate reserve; MVIS = maximum voluntary isometric strength; MVC = Maximum voluntary contraction; LE = Lower extremity; UE = Upper Extremity; ADL = Activity of daily living
REFERENCES


