“Contemporary Treatment and Management of Charcot-Marie-Tooth Disease: Embracing the *Exercise Is Medicine*™ Model”

Robert D. Chetlin, PhD, CSCS, CHFS
West Virginia University School of Medicine
Departments of Human Performance & Neurology
Morgantown, WV

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CMT: Exercise Treatment

Background/Introduction

• Charcot-Marie-Tooth (CMT) Disease is most commonly inherited peripheral neuropathy\(^5,10\)
  – affects 1-in-2,500 persons\(^5,10\)
  – dx via EMG study (NCV) or genetic assay
  – also known as Hereditary Motor and Sensory Neuropathy (HMSN)

• CMT first discovered circa late 1880s
  – Martin Charcot, Pierre Marie, Howard Henry Tooth

• To date, 36 loci and ~24 genes implicated in appearance of CMT\(^26,29,30\)
  – ~30+ types/subtypes of CMT
    • most common form is CMT1a (~70% of all CMT cases)
    • caused by genetic mutation, duplication, deletion
    • adverse effects: myelination, axonal transport, Schwann cell differentiation, signal transduction, mitochondrial function, endosomal translation, DNA repair\(^26,29,30\)
    – mode of inheritance includes autosomal dominant, autosomal recessive, or X-linked\(^5,10\)

• Disease expression includes muscle atrophy, distal LE weakness, UE weakness, repeated ankle sprains, abnormal gait, chronic pain & fatigue\(^4,11,34\)
  – non-terminal disorder, but *psychosocial impact similar to stroke patients*\(^24\)
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Background/Introduction (cont.)

- No cure exists
  - historical treatment limited to disease management and attenuation of known impairment
    - surgical procedures (e.g. orthodeses), orthotics (e.g. AFOs)\textsuperscript{4,36}
    - “defensive” counseling…

- CMT research studies have examined various interventions
  - drugs\textsuperscript{4,23}
    - prednisone, neurotrophin-3
  - nutritional supplements\textsuperscript{4,23}
    - creatine monohydrate, curcumin, vitamin C, coenzyme Q10
  - exercise/physiotherapy\textsuperscript{1,6,7,14-18,21,27,34}
    - resistance training
    - \textit{endurance-like} training

- Exercise has demonstrated \textit{reliable} effectiveness across CMT studies\textsuperscript{14,15,34}…
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**Literature Synopsis: Exercise & CMT**

- CMT patients *not* typically referred to exercise or physiotherapy professionals
- Few randomized controlled trials have examined exercise as tx for CMT
  - vast majority of studies (last ~20 years) have examined *resistance training* effects
    - improvements noted in muscular strength (mostly proximal muscles), functional ability (timed motor performance), muscle morphology (fiber size, muscle proteins)
    - early finding established *link between strength and functional ability* in CMT patients
      - *increased strength positively correlated to improved ADL performance*
    - *endurance-like* training improves aerobic capacity ($\text{MVO}_2$), body composition, co-morbid disease risk
- Resistance exercise protocol specifics (i.e. training variables) *non-uniform* from study-to-study
  - duration ranges from 8-24 weeks$^{1,6,7,14-18,21,27,34}$
  - intensity ranges from low-to-high$^{1,6,7,14-18,21,27,34}$
  - mode (exercise type) specificity and exercise volume (reps & sets) *highly* variable
    - number of exercises, upper and lower body exercises, exercise “model” (e.g. conventional, interval, “periodized”)$^{1,6,7,14-18,21,27,34}$
    - frequency fairly *consistent*
      - exercise usually performed on three non-consecutive days per week$^{1,6,7,14-18,21,27,34}$
    - progression *rarely* described…
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Literature Synopsis: Other Exercise Considerations

- Adult CMT patients are sedentary, have poor body composition, high BMI, poor exercise tolerance/capacity, increased risk of coronary artery disease and type 2 diabetes\(^6\)
  - exercise capacity in CMT patients measured at 5.7 METS\(^6\)
    - twice the *all-cause mortality risk* versus peak capacity of at least 8 METS\(^{22}\)
    - a 1 MET *increase* in exercise capacity translates to \(~11\% \text{ reduction in all-cause mortality rate and } \sim 5\% \text{ reduction in health-care cost associated with inactive lifestyle}^{22,28}\)
      - physical inactivity and obesity account for \(~10\% \text{ of United States health-care expenditures}^{33}\)
  - Review of literature indicates that most CMT patients can *safely* participate in regular exercise
    - provided contraindications to exercise *not* present\(^{16,31}\)
      - known cardiopulmonary disease\(^{12}\)
      - poorly controlled diabetes or hypertension\(^{12}\)
      - severe orthopedic limitations
        - accommodation still possible with appropriate exercise modes\(^{16}\)
      - debilitating weakness (i.e. \(<15\% \text{ of normal MVIS}\))
        - accommodation still possible, however, very weak patients may not derive benefit similar to those patients with greater baseline strength\(^{16}\)
The CMT Exercise “Conundrum”: Now What?

- Literature identifies NO standardized exercise or physiotherapy guidelines for treatment or management of CMT...
- Yet patients at increased risk for functional loss, compromised independence, lower quality of life, and incurrence of comorbid disease...
- Scientifically-based exercise/activity option for patients with chronic disease, including CMT – supported by recognized allied health entities – IS available to clinicians$^{25,31}$...
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CMT Exercise Prescription: The “Exercise-Is-Medicine™” Model

- Exercise-Is-Medicine™ (EIM) designed to incorporate activity assessment and exercise/activity prescription, when appropriate, as standard clinical operating procedure in prevention and treatment of disease\textsuperscript{25,31}
  - Endorsed by American Medical Association, American Heart Association, American College of Sports Medicine, United States Department of Health and Human Services, and the Office of the United States Surgeon General
  - Specified organizations recommend that children and adults with chronic disease and disability (including CMT), whom are capable, should regularly participate in exercise and activity
  - Patient literature, clinic literature, support information readily available…

www.ExerciseIsMedicine.org
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**EIM Summary: General Exercise Guidelines for Children with CMT**

- Programs should include emphasis on muscle strength, bone strength, endurance, and balance…
- 3 days of moderately-vigorous exercise and activity per week, ~30 minutes/day recommended
  - emphasis on age-appropriate, non-contraindicated, and *fun* activity…
- Account for *individual limitations* to minimize *injury risk exposure*…
  - primarily, impairment of motor control and sensory awareness of LE (re: ankle & foot)
  - activities emphasizing running and jumping (re: repeated *open-chain* and *closed-chain* actions) could be *contraindicated*
  - prescribed orthopedic braces should be worn during exercise and activity
- Exercise and activity examples for CMT pediatric populations:
  - bicycle riding (consider *tandem* riding…)
  - catching and throwing
  - swimming
  - resistance exercise (body weight, bands, machines, hand-held weights)
  - “*exer-games*” (Wii, Playstation, Xbox)
  - lower-intensity martial arts (tai-chi)
  - *PLAY*…
EIM Summary: General Exercise Guidelines for *Adults* with CMT\textsuperscript{31}

- Programs should include emphasis on muscle strength, bone strength, endurance, and balance…
- 150 minutes/week of moderate to moderately-vigorous aerobic exercise and activity per week, ~30 minutes/day recommended
  - bouts 10 of *at least* minutes duration spread over each week
- Muscle/bone strengthening at least 2x/wk
  - emphasize *simultaneous use of all major muscle groups*
- Account for *individual limitations* to *minimize injury risk exposure*…
  - motor and sensory impairment, repeated open-chain/closed-chain actions, use of prescribed orthopedic braces
- Exercise and activity examples for CMT adult populations:
  - riding or rowing
  - swimming and water aerobics
  - vigorous gardening (digging, lifting) & household chores
  - resistance exercise (body weight, bands, machines, hand-held weights)
  - low-impact balance and flexibility training (yoga, tai chi)
- *At the very least, avoid inactivity*…
  - reduce co-morbid disease risk, maintain muscle mass & bone health, reduce incidence of falling, maintain functional independence & higher QOL…
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CMT Exercise & Activity: Nutritional Considerations

- *No* studies have examined nutritional/dietary needs associated with exercising, active CMT patients
- Individual modifications likely indicated
  - should be based on known relative energy and metabolic requirements for exercise and activity
    - consider mode, duration, frequency, volume, and intensity of exercise/activity…
- Reasonable foundation: *“balanced” diet* for active people…
  - ~12-15% protein, ~25-30% fat (~75-90% unsaturated), ~55-60% carbohydrate
  - daily energy intake for active persons ~1.5-1.7x’s total daily energy expenditure (~35-40 kcal/kg bwt/day)
- *Acute* exercise/activity considerations…
  - necessitates adequate fluid, macronutrient intake before, during, and after exercise/activity
    - “before”: 400-600 ml fluid (~14-22 oz); snack (higher carbs, moderate protein, low fat/fiber); 1-2 hours prior to exercise/activity
    - “during”: 150-350 ml fluid (~6-12 oz) consumed regularly (~15-20 mins apart); 4-8% carb solution maintains blood glucose
    - “after”: 450-675 ml fluid (~16-24 oz) for each pound of lost body weight; ingest carbs & protein to replenish glycogen and facilitate muscle “repair”
  - Adjustments should be made based upon individual patient circumstances and level of activity…
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EIM Application in CMT: A “Back to the Future” Case Study

• Long-term Effects of Exercise and Activity Prescription in Children with CMT
  – Purpose: to evaluate the effects of a one-year exercise and activity prescription combining resistance training and endurance training in two children with CMT
  – Methods: resistance training with exercise bands (3 days/week); endurance training with exergames (3 days/week)
    • outcomes: muscular strength (QMA); body composition (DEXA); MVO₂ (bicycle GXT); postural stability, and; heart disease risk factors (e.g. blood lipids)
  – Results (% change):
    MVIS (kg):
    UE Total = +8%; LE Total = +1.5%; ankle dorsiflexion = +10%
    DEXA:
    BMD (g/cm²) = +3%; LM (kg) = +3%; FM (kg) = +0.3%; TM (kg) = +5%; BF% = -1.5%
    GXT:
    Total Exercise Time (min) = +50%; Time to MVO₂ (min) = +53%; MVO₂ (ml/kg/min) = +1.5%
    Lipids (mg/dl):
    TGs = -52%; LDLs = -22%; TC = -22%
    Postural Stability…
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Long-Term Exercise/Activity Rx in Children with CMT

Postural Stability Results (girl, 16 years old)

**Pre-test**

RHYTHMIC WEIGHT SHIFT TEST

- Left/Right
- Front/Back

SLOW (3 sec per transition)

deg/sec | On-Axis Velocity | % Directional Control
---|---|---
L/R | 1 | 56
F/B | 4.0 | 31
Comp | 3.0 | 11

**Post-test**

RHYTHMIC WEIGHT SHIFT TEST

- Left/Right
- Front/Back

SLOW (3 sec per transition)

deg/sec | On-Axis Velocity | % Directional Control
---|---|---
L/R | 79 | 2.2
F/B | 72 | 2.1
Comp | 78 | 2.1

Data Range Note: No Data Range.

Post Test Comments:
Long-Term Exercise/Activity Rx in Children with CMT
Postural Stability Results (girl, 16 years old)

**Pre-test**

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Post Test Comments:
CMT: Exercise Treatment

Long-Term Exercise/Activity Rx in Children with CMT
Postural Stability Results (girl, 16 years old)

### Pre-test

**Limits of Stability Test**

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<th>RT (sec)</th>
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<th>EPE (%)</th>
<th>MXE (%)</th>
<th>DCL (%)</th>
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100% LOS

### Post-test

**Limits of Stability Test**

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100% LOS

### Data Range Note: No Data Range.

Post Test Comments:

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Future Research Considerations

- **Integrate EIM into contemporary CMT research...**
  - evidence indicates that exercise/activity rx effectively used across clinical domains (e.g. type 2 diabetes, cardiac rehab, orthopedic rehab, hypertension, cancer, aging)\(^{25}\)
  - evidence indicates that exercise/activity rx improves patient sensitivity to various drugs (e.g. cardiac, antihypertensive, hypoglycemic), demonstrating *permissive* effect between exercise and certain pharmaceutical agents\(^{13,19}\)

- **Address funded research “disconnect”...**
  - government and reputable allied health agencies strongly endorse EIM model and promote H&HS Physical Activity Guidelines for All Americans, *yet*...
  - NIH has funded *NO* study examining the effects of exercise and/or activity in adults or children with CMT\(^{8}\)

- **Account for patient concerns...**
  - Promote and conduct research patients can *directly* identify with...

*What might such a contemporary research model look like?*
The Bi-Directional Translational Model…

“Functional Envelope” Outcomes
Re: Integrated Physiology

- PERFORMANCE: isometric (static); SSC (dynamic); work (function)
- LOCALIZATION: histopathology/immunolabeling (muscle, nerve)
- QUANTIFICATION: stereology (% tissue fraction) & gene expression
- DISTRIBUTION: regionalization & differentiation

BASIC…

- Control of “Biomechanical Loading Signature”
  - duration, frequency, velocity, duty cycle (i.e. work/rest), reps/sets, ROM

RESPONSE TITRATION…

- Refinement of loading signature & outcomes
  - “Bi-Directional”…

TRANSLATIONAL…

- Human Dynamometer (BTE): Non-Injury, Adaptive Protocol
- Adaptive Training Regimen & Loading Evaluation
  - duration, velocity, duty cycle, reps/sets, ROM, force, torque
  - “Functional Envelope” outcomes…
  - other outcomes (e.g. body comp, MVO₂)

Additional “Factors”/Evaluation of Permissive Effects
- Age (young vs. old)
- Diet (nutritional supplements)
- Pharmacologic agents (neurotrophic drugs)

SSC Mechanical Loading: EXERCISE

NIOSH Rodent Dynamometer²,³,⁹: Non-Injury, Adaptive Protocol

Human Trials…

Transgenic CMT1a Rat²⁶

Additional images and diagrams related to physiology and mechanobiology.
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References

QUESTIONS?