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

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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*\(^24\)
CMT: Exercise Treatment

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 (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\textsuperscript{1,6,7,14-18,21,27,34}
  - intensity ranges from low-to-high\textsuperscript{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”)\textsuperscript{1,6,7,14-18,21,27,34}
  - frequency fairly *consistent*
    - exercise usually performed on three non-consecutive days per week\textsuperscript{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 *\(~11\%\) reduction in all-cause mortality rate* and *\(~5\%\) reduction in health-care cost* associated with *inactive lifestyle*\(^{22,28}\)…
    - physical inactivity and obesity account for *\(~10\%\) 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\% 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…
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*\(^{31}\)

- 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*…
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EIM Summary: General Exercise Guidelines for Adults with CMT

- 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...
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); MVO$_2$ (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/cm$^2$) = +3%; LM (kg) = +3%; FM (kg) = +0.3%; TM (kg) = +5%; BF% = -1.5%
    - **GXT**:
      Total Exercise Time (min) = +50%; Time to MVO$_2$ (min) = +53%; MVO$_2$ (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

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

Pre-test
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Post-test
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Post Test Comments:
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Long-Term Exercise/Activity Rx in Children with CMT

Postural Stability Results (girl, 16 years old)

Pre-test

Post-test
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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…

**Bi-Directional Translational Model**

- **Transgenic CMT1a Rat**: NIOSH Rodent Dynamometer: Non-Injury, Adaptive Protocol

  - **SSC Mechanical Loading**: EXERCISE
    - 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”

- **“Functional Envelope” Outcomes**
  - **Performance**: isometric (static), SSC (dynamic), work (function)
  - **Localization**: histopathology/immunolabeling (muscle, nerve)
  - **Quantification**: stereology (% tissue fraction) & gene expression
  - **Distribution**: regionalization & differentiation

- **BASIC**

- **Translational**
  - Human Dynamometer (BTE): Non-Injury, Adaptive Protocol

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

- **Human Trials**

  - **Adaptive Training Regimen & Loading Evaluation**
    - Duration, velocity, duty cycle, reps/sets, ROM, force, torque
    - “Functional Envelope” outcomes…
    - Other outcomes (e.g., body comp, MVO₂)
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References

QUESTIONS?