Strength testing in NF

REiNS Summer 2017 Meeting

June 13, 2017

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Response Evaluation In Neurofibromatosis & Schwannomatosis

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INTERNATIONAL COLLABORATION

Acknowledgements

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CTF

- Scott Plotkin
- Brigitte Widemann
- Kaleb Yohay
- Andrea Gross
- Jaishri Blakeley
- Michael Fisher
- Judith Goldberg
- Nashwa Khalil
- Barbara Johnson
- Heather Thompson
- Ann Blanton
- Simone Ardern-Holmes
- Dusica Babovic
- Andrea Baldwin
- Fred Barker
- Rebecca Betensky
- Joni Doherty
- Rachel Ershler
- Gareth Evans
- Rosalie Ferner
- Kathy Gardner
- Tessa Hadlock
- Chris Halpin
- Trent Hummel
- Allen Julian
- Chris Moertel
- Rebecca Mullin
- Kent Robertson
- Betty Schorry
- Carolyn Sidor
- William Slattery
- James Tonsgard
- David Viskochil
- Ute Wahllander
- Brad Welling
- David Wolf

Overview

- Outcome measures for assessing muscle strength
  - Srivandana Akshintala, David Stevenson
- Dysphagia outcome measures
  - Heather Thompson, Ann Blanton

Project Outline

- A multi-institution prospective study of using hand held dynamometry for quantitative muscle strength testing in children and adults with NF
- Objective: To assess the reliability of measuring muscle strength using HHD to evaluate its utility as an outcome measure in clinical trials
  - Measure intra-observer and inter-observer variability in force generated by select muscle groups using a HHD

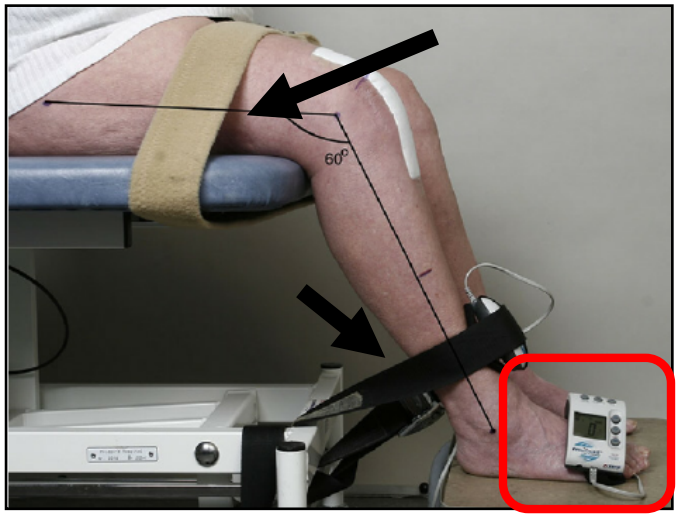
Background and rationale

- Muscle weakness has been described in NF1*
  - primary myopathy, central nervous system dysfunction, or due to abnormalities of peripheral nerves
- Clinical trials targeting PNs in children with NF1 have anecdotally shown to decrease functional impairments including muscle weakness
- Functional outcome measures are therefore needed to assess clinical benefit, in particular, muscle strength

*Souza et al 2009, Johnson et al 2011, Cornett et al 2015

HHD instrument

- Hand held dynamometry measures force generated by an individual muscle in Newtons



Common muscle groups:
Shoulder: abduction, extension, external rotation
Elbow: flexion, extension
Wrist: extension
Hip: flexion, extension, abduction
Knee: extension, flexion
Ankle: dorsiflexion, plantar flexion

HHD clinical studies

- Reproducibility of strength measurements using a HHD has been studied in many patient populations*
  - healthy children, children with cerebral palsy, Duchenne muscular dystrophy, and juvenile chronic arthritis
  - intraclass correlation coefficient >0.73 with performance varying based on patient population and muscle group being tested
- Strength testing using a HHD has also been used as an efficacy measure in clinical trials for amyotrophic lateral sclerosis**

*Hedengren et al 2001, van den Beld et al 2006, Macfarlane et al 2008, Hebert et al 2015, Brussock et al 1992, Berry et al 2006, Hebert et al 2011 **Shefner et al 2016

HHD in NF

- Advantages
  - measure isometric muscle strength in various muscle groups in upper and lower extremities
  - Testing of each muscle group takes few min (4 muscle groups ~15-20 min)
  - Testing can be performed in clinic setting
  - Does not use testing till exhaustion
- Limitations
  - Ceiling effect for strong muscles (subject overcomes strength of examiner)
  - Variable phenotype in NF

Study design

- Eligibility:
  - Patients with clinically confirmed NF per NIH clinical diagnostic criteria or a known NF mutation
  - Age ≥ 5 years
  - Able to follow instructions and cooperate with exam to assess strength
  - No orthopedic procedure or other major surgery that could influence extremity strength in past 6 months
  - No tibial dysplasia

Study design

- Strength assessed in specific muscle groups
- Measurement by physical therapists or other trained clinicians
- Standardized test protocol define the correct pt positioning, HHD placement, stabilization of the limb, and order of muscle testing
- A “make test” will be used
- Three repetitions will be performed per session and average used
- A repeat session performed with 3 repetitions by same and/or different examiner#
- Clinical data collected:
  - age, sex, weight, height, handedness, muscle strength by MRC scale
  - h/o NF manifestations including presence of spinal or peripheral nerve tumors, CNS manifestations, ADHD, skeletal deformities, prior surgeries

Study design

- Potential muscle groups to evaluate

Muscle	Test	Root
Gluteus maximus	Hip ext	L5, S1
Iliopsoas	Hip flex	L1, L2
Gluteus medius	Hip Abd	L4, L5
Hamstring	Knee flex	L5, S1
Plantar flexors	Plantar flex	S1, S2
Deltoid	Shoulder Abd	C5
Biceps	Elbow flex	C6
Triceps	Elbow ext	C7
Wrist ext	Wrist ext	C6, C7

Usual design - study same muscles in all

- Eligibility: Pediatrics (<16 yrs) ± Adults*
- At least 1 muscle group with <5/5 by MRC (enriches for patients with weakness)
- Identify 2-3 muscle groups in upper and lower extremity to evaluate in all patients (left or right side for each muscle) – total 4-6 muscles; exam time 15-30 min
- If there is a clinically relevant weak muscle not in the picked 4-6 muscles, can measure those and analyze separately
- Adv: can analyze variability for each muscle group. Can also separately analyze muscles that are weak by MRC and not
- Disadv: Concern with increased variability in adults with muscles that have 5/5 strength (ceiling effect). Testing muscles that may not be potentially of interest

Design 2- study weak muscles only

- Eligibility: with at least 1 muscle group with <5/5 on MRC and study cohorts are divided by muscle groups to be studied
- Pediatric (<16 yrs) and adults
- 1 patient could be in multiple cohorts based on # muscles that are weak
- Plan to also analyze all weak muscles together
- Adv: can analyze variability for each muscle group in the population of interest and overcomes ceiling effect concerns
- Disadv: finding adequate numbers of patients and need to screen more patients to identify patients of interest

Design 3 - study affected limb only

- Eligibility: with at least 1 weak muscle
- Patients in 2 cohorts – Upper extremity (UE) or lower extremity (LE)
- Pediatric (<16 yrs)/Adults
- Identify 3-4 muscles for UE and 3-4 for LE of the involved side and measure those in respective cohorts. Patients in each cohort have all the same muscles tested
- Analyze for each muscle group, and all weak muscles together
- Adv: can analyze variability for each muscle group in the population of interest with enrichment for weak muscles as good chance of multiple muscles in an extremity being weak
- Disadv: same issues with ceiling effect and variability and potentially testing muscles not of interest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Design- Affected limb based on PN

- Eligibility: with PN involving either UE or LE (can be unilateral or bilateral). Pts in 2 cohorts – UE or LE
  - Pediatric patient (<16 yrs)
  - Adults
- Pick 3-4 muscles for UE and 3-4 for LE and measure those in respective cohorts
- Adv : can analyze variability for each muscle group in the population of interest assuming trials for PNs
- Disadv: Tumors may not correlate with weakness. Including weak + not weak muscles may lead to same issues with ceiling effect and variability