Gait and Balance Disturbance in Pediatric Cancer Survivors With Neuropathy

Laura Gilchrist PT, PhD
Lynn Tanner PT, MPT

Pediatric Oncology Intro
• Comprise 2% of all cancer cases in the U.S.
• Leading cause of death from disease of children in the U.S.
  ▫ 2nd in adults
• Mortality rates
  ▫ 2.4 per 100,000 in children ages 1-4
  ▫ 2.5 per 100,000 in children 5-14
  ▫ Rate of cancer in age 15-29 3x higher than below 15
• Overall 5-year survival rate of 81%

Common Pediatric Cancers
• Acute Lymphoblastic Leukemia (ALL)
• Acute Myelogenous Leukemia (AML)
• CNS Tumors
• Lymphoma
  ▫ Hodgkins
  ▫ Non-Hodgkins
• Solid Tumors
  ▫ Wilms’ Tumor
  ▫ Rhabdomyosarcoma
  ▫ Osteosarcoma, Ewings Sarcoma

Pediatric Cancer Treatments
• Chemotherapy commonly used
  ▫ +/- Surgery
  ▫ +/- Radiation
• Chemotherapy Side-effects
  ▫ Nausea – multiple agents
  ▫ **Neurotoxicity** – multiple agents
  ▫ Pulmonary Toxicity – Ankylyating agents
  ▫ Cardiotoxicity – Anthracyclines
  ▫ Muscle Weakness - Corticosteriods
  ▫ Osteonecrosis - Corticosteriods

Neurotoxicity
• Chemotherapy-induced peripheral neuropathy (CIPN)
  ▫ Estimated to occur in 80-90% of pediatric patients with cancer (Gilchrist & Tanner 2013)
  ▫ Often under-reported (Markman 2006; Hausheer et al 2006; Gilchrist et al, 2013)
  ▫ Result of direct damage peripheral nerves
    ▫ Sensory, Motor, Autonomic
    ▫ Mild motor deficits are frequent
  ▫ Longer axons more susceptible
  ▫ Drug effects tend to accumulate
    ▫ Distally predominant CIPN “stocking glove” distribution
    ▫ Often begins in lower extremities and later appears in upper extremities

2 commonly used neurotoxic agents

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Vincristine</th>
<th>Cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Lymphocytic Leukemia (ALL)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Non-Hodgkin’s Lymphoma</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Hodgkin’s Lymphoma (low &amp; int risk)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hodgkin’s Lymphoma (high risk)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid Tumors: Wilm’s (kidney), Rhabdomyosarcoma (muscle) Ewings (bone), Neuroblastoma (adrenal), Osteosarcoma (bone)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CNS (brain tumors)</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
Other agents with potential neurotoxicity

- Other forms of vinca alkaloids
- Other forms of platinum-based therapy
- Bortezomib
- Bevacizumab
- Thalidomide
- Etoposide
- Taxanes

- Agents with CNS activity
  - IT therapy
  - Oxaliplatin crossing into CSF

Pathophysiology of Peripheral Neuropathy

- Vincristine
  - Disrupts the microtubules (building blocks of axons)
  - Causes degeneration of the axon cytoskeleton → decreased axonal transport
  - Glial activation – astrocytes and microglia
  - Mitochondrial dysregulation
- Cisplatin
  - High concentrations found in DRG cell bodies
  - Oxidative Stress to PNS neurons
  - Damage to glial cells and dissociation of glial cells from the axon

Potential modifiers of CIPN

- Genetics
  - CEP72 (Diouf et al, JAMA 2015)
  - ACTG1 (Ceppi et al, Pharmacogenomics 2014)
  - CYP3A5 – mixed results
- Pre-existing neuropathy
- Nutritional status
  - Vitamin E and prealbumin serum levels (Velasco et al, J Peripheral Nerv Syst 2016)
- Vit D levels
  - Bortezomib and/or thalidomide (Wang et al, Support Care Cancer 2016)
- Dosing schedules
  - Every three weeks vs. weekly Taxane + Carboplatin reduced sensory neuropathy (Chan et al, NEJM 2016)

Potential Impact of Neuropathy

- Gait
- Balance
- Manual Dexterity
- Neuropathic Pain
- QOL
- Delayed motor development during treatment?

Measuring Neuropathy

- How do we measure neuropathy in pediatric population?
- Ped-mTNS - for children 5 years and older
- Comprised of:
  - Subjective report of symptoms
  - Clinical Examination of:
    - Pin sensibility
    - Vibration sense
    - Strength
    - Deep Tendon Reflexes

Grading

Based on extent of symptoms/loss since CIPN is thought to be a length-dependent neuropathy:

Pin Sensibility: _______

0  Normal
1  Reduced in fingers/toes
2  Reduced up to wrist/ankle
3  Reduced up to elbow/knee
4  Reduced above elbow/knee
Ped-mTNS by Diagnostic Categories

<table>
<thead>
<tr>
<th>Ped-mTNS score</th>
<th>Cases (n=41)</th>
<th>Controls (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ped-mTNS score</td>
<td>8.68 +/- 4.16**</td>
<td>1.44 +/- 0.90</td>
</tr>
<tr>
<td>Subjective symptoms</td>
<td>% with deficit</td>
<td>% with deficit</td>
</tr>
<tr>
<td>Sensory Symptoms</td>
<td>27%</td>
<td>2%</td>
</tr>
<tr>
<td>Motor Function</td>
<td>49%</td>
<td>10%</td>
</tr>
<tr>
<td>Autonomic Symptoms</td>
<td>37%</td>
<td>39%</td>
</tr>
</tbody>
</table>

** p<0.001  * p<0.05

Clinical Testing

<table>
<thead>
<tr>
<th>Clinical Testing</th>
<th>Cases (n=41)</th>
<th>Controls (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light Touch</td>
<td>% with deficit</td>
<td>% with deficit</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>Mean</td>
</tr>
<tr>
<td>44%</td>
<td>1.12**</td>
<td>5%</td>
</tr>
<tr>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pin Sensation</td>
<td>46%</td>
<td>32%</td>
</tr>
<tr>
<td>0.51</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>Vibration</td>
<td>37%</td>
<td>2%</td>
</tr>
<tr>
<td>0.73*</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Strength</td>
<td>98%</td>
<td>39%</td>
</tr>
<tr>
<td>1.88**</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>Deep Tendon Reflexes</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>2.60**</td>
<td>0.00</td>
<td></td>
</tr>
</tbody>
</table>

Neuropathy and Function

- Neuropathy and Balance \( r_s = -0.626, p < 0.001 \)
- Neuropathy and Manual Dexterity \( r_s = -0.461, p < 0.001 \)

Recovery of CIPN

- Followed subjects at 3 and 6 months post-treatment (n=67)
  - ALL, Lymphoma, Other solid tumors (primarily Wilms’)
- At 6 month follow-up % population > 4
  - ALL 11.5%
  - Lymphoma 57%
  - Other solid tumors 60%

Recovery of specific impairments

<table>
<thead>
<tr>
<th>Impairment</th>
<th>On Treatment</th>
<th>6 Months Post Treatment</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light Touch Abnormality</td>
<td>38.8%</td>
<td>15.4%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Vibration Abnormality</td>
<td>25.0%</td>
<td>11.9%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Ankle Dorsiflex Weakness</td>
<td>77.6%</td>
<td>26.9%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Great Toe Extension Weakness</td>
<td>88.1%</td>
<td>59.7%</td>
<td>9.8%</td>
</tr>
</tbody>
</table>
Recovery of Balance Control

- Balance scores improved as a group but never to population norms
  - 7.4 ± 3.3 initial, 9.1 ± 3.3 3 month, 10.3 ± 3.9 6 month
  - F=11.75, p<0.001, effect size=0.32
- Neither diagnosis nor treatment were associated with balance recovery
- 82% received PT intervention

Population

- Children and adolescents 5 years of age or older
  - Treated with vincristine
  - Acute Lymphoblastic Leukemia (ALL), Hodgkins or non-Hodgkins lymphoma, or other solid non-CNS tumors
  - Ped-mTNS score > 4
- Excluded: bony or muscle tumors of the lower extremity, tumors impinging on the spinal cord, osteonecrosis of lower extremity
- Age- and gender-matched controls

Gait changes in vincristine neuropathy

- Purpose: To determine if gait changes were frequent in children with vincristine-related CIPN
- We know that children undergoing vincristine treatment develop CIPN
  - Light Touch
  - Distal Strength
  - DTRs
  - Mild balance deficits
- Does this impact gait characteristics?
- If present:
  - Most frequent changes noted
  - Underlying impairments

Methods

- Height, weight, BMI, and leg length
- Ped-mTNS – neuropathy scale
- Ankle DF ROM – passive and active
- Balance and Strength subtests of the BOT-2
- Gait analysis – GaitRite System
  - Barefoot, at self-selected “normal” walking speed
  - 2 trials averaged
- 6 MW test
  - Measure walking capacity
  - Potential to induce fatigue-related gait changes
- Immediate repeat of Gait analysis as previous

Results

<table>
<thead>
<tr>
<th></th>
<th>Neuropathy (n=52)</th>
<th>Control (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>11.3 ± 4.5</td>
<td>11.3 ± 4.5</td>
</tr>
<tr>
<td>Gender (% Male)</td>
<td>42.3%</td>
<td>42.3%</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>146.0 ± 23.2</td>
<td>145.3 ± 21.8</td>
</tr>
<tr>
<td>BMI Percentile</td>
<td>62.7 ±28.2*</td>
<td>48.7 ± 27.3</td>
</tr>
<tr>
<td>Leg Length (R/L) (cm)</td>
<td>73.4 ± 12.4 / 73.4 ± 12.3</td>
<td>72.4 ± 12.1 / 72.3 ± 11.8</td>
</tr>
<tr>
<td>Neuropathy Score</td>
<td>10.6 ± 4.0*</td>
<td>1.2 ± 1.3</td>
</tr>
<tr>
<td>Vincristine Cumulative Dose</td>
<td>17.5 ± 8.8 mg/m²</td>
<td>NA</td>
</tr>
<tr>
<td>Ankle DF AROM (R/L)</td>
<td>3.5 ± 7.5° / 3.2 ± 6.7°</td>
<td>11.4 ± 5.4 / 11.9 ± 5.4</td>
</tr>
<tr>
<td>Ankle DF PROM (R/L)</td>
<td>7.8 ± 6.5° / 7.2 ± 6.3°</td>
<td>15.2 ± 5.0 / 15.3 ± 5.6</td>
</tr>
<tr>
<td>BOT-2 Balance Subscore</td>
<td>8.5 ± 3.5°</td>
<td>13.7 ± 4.3</td>
</tr>
<tr>
<td>BOT-2 Strength Subscore</td>
<td>10.9 ± 4.4°*</td>
<td>16.4 ± 3.3</td>
</tr>
</tbody>
</table>

* p<0.05
Linear Regression Analysis

- Self-selected Velocity
  - Step length ($r=0.76$), cadence ($r=0.66$)
  - Major deviation for multiple linear regression models
- Step Length
  - 2 impairments with unique contributions explained 45.1% of variability ($F=12.88, p<0.001$)
  - Active ankle DF ROM ($\beta=0.25, p=0.009$)
  - Balance sub-scale score ($\beta=0.31, p=0.001$)
- 6MW Z scores
  - 3 impairments with unique contributions explained 73.0% of variability ($F=37.74, p<0.001$)
  - Strength subtest BOT-2 ($\beta=0.43, p<0.001$)
  - Ped-mTNS score ($\beta=-0.26, p<0.001$)
  - Normalized velocity pre-6MW ($\beta=0.18, p=0.024$)

Discussion

- Children with vincristine-related neuropathy have:
  - Decreased self-selected velocity
    - Related to decreased step length not cadence
  - Decreased step length
    - Associated with decreased ankle DF ROM and Balance
  - Changed foot fall characteristics after 6MW test
    - Increased % forefoot in contact – “foot slap”
    - Increased % of heel contact and whole foot contact
  - Decreased performance on 6MW testing
    - Associated with general strength, neuropathy score, and self-selected gait velocity prior to testing

Gait Assessment and Intervention in Children and Adolescents with non-CNS Cancer
Lynn Tanner, PT
Children’s Hospitals and Clinics of Minnesota
612-813-6274
Children vs. Adults

ROM available in our study participants: 7°

Initial Contact

• Observations
  - Decreased dorsiflexion clearance
  - Foot slap
  - Flat foot contact
  - No heel contact (toe-walking)
  - Increased knee flexion

Loading Response

• Observations
  - Pronated/Out-toed foot position
  - In-toed foot position

Midstance

• Observations
  - Pronated foot position
  - In-toeing/Out-toeing
  - Plantarflexed foot
  - Knee hyperextension
  - Increased anterior pelvic tilt
  - Hip IR/ER

Terminal Stance

• Observations
  - Decreased push off
  - Abnormal foot position
  - Early heel rise
Pre-Swing

• Observations
  - Plantarflexed ankle
  - Increased hip flexion

Initial swing – Mid swing

• Observations
  - Decreased time in phase
  - Ankle plantarflexion
  - Increased hip flexion

Terminal swing

• Observations
  - Plantarflexed foot
  - Knee flexion
  - Increased hip flexion

ROM Assessment

• Hip/knee/great toe screen
• Hamstring length
• Ankle
  - Prone
    - Knee extended
    - Knee flexed

Strength Assessment

• Core/hip/knee
  - MMT
  - Supine to sit
  - Floor to stand
  - Stairs
  - Ankle
    - MMT
    - Dynamometry (if available)
• Toes
  - Great toe extension

Neuropathy and Balance Assessment

• Ped-mTNS
• Balance assessment
  - Single leg stance
  - Bruininks-Oseretsky Scale of Motor Performance Balance subscale
**Pain**

- Age-appropriate pain scale
- Pain today
- Pain in last month
- Activity during pain
- Relieving factors
- Ask child and parents

**Other factors**

- Activity level
  - Lansky scale/Karnofsky scale
  - Godin-Leisure Scale
  - Activity monitors
  - Consider parents’ perspective
- Treatment phase
  - IP/OP
  - Dosing of neurotoxic agents
- Co-morbidities
  - Osteonecrosis

**Gait goal**

- Demonstrate a heel-toe gait pattern for an age-appropriate distance in a 6 MWT in order to... (run errands with family, play with sibling, patient goal here etc)
  - Increase step length to xxx by xx/xx/xx to be within 1 S.D. of age norm to allow (patient goal here)
- Variables
  - Gait pattern
  - Aerobic capacity
  - Muscular endurance
  - Etc.

**Stretching/Strengthening/Gait training**

- Mild motor CIPN
  - >10° in young/school-age
  - >5-10 in adolescents
- Induction phase
  - New in maintenance
  - Relatively active or increasing activity
  - Fair to good home exercise compliance

**Stretching**

- Other
  - Hamstring
  - Hip

- Manual stretching
  - Young
  - Sedentary
  - Poor tolerance
- Gastrocsoleus stretch
  - Wall stretch
  - Stair stretch
  - Yoga postures (downward dog)
  - Incline stretch
**Strengthening**
- Peripheral strengthening
  - Heel walking
  - Standing DF hold with object balance
  - Tip toe statues
  - Jumping high for push off
  - Jumping down-eccentric control
  - "Toe grasping"
  - Dorsiflexion tug-war
  - DF with 1-3# barbell in stride stance
- Hip and core strengthening
  - Deep squat controlled
  - Squat walk
  - Many more!

**Gait training**
- "Quiet walking"
- "Squish the bugs walk"
- Lengthen stride length
- T-band just below knee for toe walking
- Balance beam dorsiflexion freeze
- Stride stance work
- Treadmill training
  - Symmetry, quality with endurance
  - Inversion - look at toe extensors, circumduction
  - Out-toeing - foot compensation or WBOS
  - ORTHOTICS

<table>
<thead>
<tr>
<th>Historical interventions</th>
<th>Historical results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily heelcord stretching</td>
<td>-Loss of ankle ROM</td>
</tr>
<tr>
<td></td>
<td>-Midfoot collapse</td>
</tr>
<tr>
<td></td>
<td>-Hindfoot valgus</td>
</tr>
<tr>
<td>Off-the-shelf dorsiflexion stretching splints night and sedentary time</td>
<td>-Maintains or slight increase in DF ROM</td>
</tr>
<tr>
<td></td>
<td>-Midfoot collapse</td>
</tr>
<tr>
<td></td>
<td>-Hindfoot valgus</td>
</tr>
<tr>
<td>Hinged AFOs worn daytime and/or nighttime</td>
<td>-Varied results in ankle DF ROM</td>
</tr>
<tr>
<td></td>
<td>-Collapsed midfoot</td>
</tr>
<tr>
<td></td>
<td>-Hindfoot valgus</td>
</tr>
</tbody>
</table>

**Orthotic Decision**

<table>
<thead>
<tr>
<th>Ankle ROM</th>
<th>Strength</th>
<th>Gait</th>
<th>Foot Posture</th>
<th>Treatment Cycle</th>
<th>Age</th>
<th>Season</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>MMT 4</td>
<td>Foot slap</td>
<td>Loss of arch</td>
<td>Early</td>
<td>Age 2-4</td>
<td>Compliance in hot weather</td>
</tr>
<tr>
<td>Speed of</td>
<td></td>
<td>Early heel rise</td>
<td>Carpal valgus</td>
<td>Middle</td>
<td>School age</td>
<td></td>
</tr>
<tr>
<td>loss</td>
<td></td>
<td>Shortened step length</td>
<td>Out-toeing</td>
<td>End</td>
<td>Adolescent</td>
<td></td>
</tr>
<tr>
<td>5-10 degree</td>
<td></td>
<td>Toe walking</td>
<td>DF ROM</td>
<td>Neurotoxic agents</td>
<td>Adult</td>
<td></td>
</tr>
<tr>
<td>Active and</td>
<td></td>
<td>Change over 6 MWT</td>
<td>Prevention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>passive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Foot</th>
<th>Posture</th>
<th>Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>Middle</td>
<td>End</td>
</tr>
</tbody>
</table>

Children's Hospitals and Clinics of MN 2015
**Decreased ankle ROM**

**Foot posture changes**

**Muscle weakness**

**Serial Casting**

**Orthotics**

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**AFO Wean**

- Decrease time in AFOs
- Change to wear them in the latter half of the day
- Continue night-time use if doing so
- Option: Wear before and after school
- Option: Wear during school and not on weekends
- Option: Wear in the latter half of the day
- Reassess after 1 month

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**Solid AFO Pilot Study**

- Inclusion: Ankle DF ≤ MMT 4, non-CNS cancer, referral for AFOs
- Wore Solid AFOs for 4 weeks
- Prescribed wear schedule 23/24 hours
- Adherence 12.31 hrs +/- 13

---

**Gait Outcomes**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pre Intervention/Barefoot to Post Intervention</th>
<th>Post Intervention/Barefoot to Post Intervention/AFO on</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step length (cm)</td>
<td>Median 49.25</td>
<td>59.16</td>
</tr>
<tr>
<td>Stride length (cm)</td>
<td>92.89</td>
<td>99.16</td>
</tr>
<tr>
<td>Velocity (cm/sec)</td>
<td>46.23</td>
<td>92.89</td>
</tr>
<tr>
<td>Cadence (Hz)</td>
<td>11.00</td>
<td>11.00</td>
</tr>
<tr>
<td>Heel to head base of support (cm)</td>
<td>303x180</td>
<td>303x180</td>
</tr>
</tbody>
</table>

---

**Characteristic**

<table>
<thead>
<tr>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>2</td>
</tr>
<tr>
<td>Male</td>
<td>4</td>
</tr>
<tr>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>Age at Diagnosis</td>
<td>4</td>
</tr>
<tr>
<td>5-7</td>
<td>2</td>
</tr>
<tr>
<td>8-11</td>
<td></td>
</tr>
<tr>
<td>Race or Origin</td>
<td>5</td>
</tr>
<tr>
<td>Caucasian</td>
<td>1</td>
</tr>
<tr>
<td>Black</td>
<td></td>
</tr>
<tr>
<td>Diagnostic Group</td>
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<tr>
<td>ALL – B cell</td>
<td>1</td>
</tr>
<tr>
<td>ALL – T cell</td>
<td>2</td>
</tr>
</tbody>
</table>

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**SMO/FO**
### Ankle Outcomes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median Pre-Intervention</th>
<th>Median Post-Intervention</th>
<th>Z value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passive ankle dorsiflexion ROM (degrees)</td>
<td>.50</td>
<td>8.00</td>
<td>-2.207</td>
<td>.027</td>
</tr>
<tr>
<td>Active ankle dorsiflexion ROM (degrees)</td>
<td>-1.00</td>
<td>1.25</td>
<td>-1.572</td>
<td>.116</td>
</tr>
<tr>
<td>Ankle dorsiflexion strength (lbs)</td>
<td>19.25</td>
<td>24.50</td>
<td>-1.992</td>
<td>.046</td>
</tr>
<tr>
<td>Great toe extension strength (MMT grade)</td>
<td>4.00</td>
<td>3.00</td>
<td>-1.966</td>
<td>.334</td>
</tr>
</tbody>
</table>

### Balance Assessments

- Single leg stance
  - Norms eyes open and closed (small n in some age groups)
    - Condon C & Cremin K 2014
- Pediatric balance scale
  - Use in younger children
    - Franjoine M et al. 2003
- Bruininks-Oesterky Scale of Motor Performance Balance subscale
  - Age 5-21
- Modified Clinical Test of Sensory Interaction on Balance
- Vestibular assessment?

### Balance intervention

- Single leg stance work
  - Step stance, kicking ball, soccer ball stop, Yoga, Wii fit, popping bubbles with feet, etc
  - Watch foot position and hip lean
- Unstable surface
  - Standing, tandem stance, single leg stance
  - Balance rocks – good for intrinsics
- Eyes closed
- Balance beam
  - Forward, backward, tandem
  - Obstacle, squat walk
  - Create your own challenge
- Dynamic gait challenges (vestibular?)

### References


