Physical Fitness in Costello Syndrome

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Outline of Presentation

• Overview of musculoskeletal problems
• Bone Density (Dr. Leoni)
• Strength
• Physical activity
What is Physical Fitness?

“Set of attributes for the ability to perform physical activity.”

Includes large number of variables (health and skill related):

1. Bone integrity
2. Metabolic
3. Muscle strength
4. Flexibility
5. Agility
6. Balance
7. Coordination
8. Cardiovascular fitness
9. Endurance
10. Body composition
11. Reaction time
12. Mental, social, emotional health
Goal: Increase Physical Fitness

Tasks:
1. What aspects are abnormal?
2. What treatments are available?
3. What treatments are most optimal?
Neurofibromatosis Type 1

NF1 (Neurofibromin)

RAS
(NRAS / KRAS / HRAS)

SPRED1

Other effector pathways (e.g., AKT/mTOR)

ERK

MEK
(MEK1 / MEK2)

RAF
(RAF1 / BRAF)

GEF
(SOS1)

GRB2

SHP2

LEOPARD

CBL

SHOC2

Noonan

Costello

Legius

Cardiofaciocutaneous (CFC)

LEOPARD

RTK

Noonan

Costello

Legius
Syndrome Overlap

NF1
- Lisch nodules
- Neurofibromas
- Optic gliomas

Legius
- Freckling

CFC
- Café au lait
- Skeletal
- Pulmonic stenosis

Ectodermal dysplasia
- Papillomata
- Loose skin

MR FTT
- Deafness
- Abnormal genitalia

Costello
- Bleeding

LEOPARD
- Noonan
Scoliosis

- Costello 17-65%
- CFC 25-33%
- NF1 10-77%
- Noonan 13-27%

Mild

Severe
Costello (scoliosis)
Costello
(Scoliosis)
Chest Wall (Pectus) Anomalies

- Costello 6-62%
- CFC 13-63%
- NF1 11-50%
- Noonan 28-95%
Bone Cysts

- Reported in NF1, CFC, Costello, and Noonan
Hip Dysplasia
(head of femur not appropriately in place)

Costello (9/22)
-several required surgery
-some permanently dislocated (wheelchair)

• Not frequent in NF1 and Noonan syndrome
flatfeet (pes planus)

- Costello 44%
- CFC 63%
- NF1 + (?%)
- Noonan + (?%)
Costello orthotics in many
Costello (Tight Heelcord)
76-82% - over half with surgery

• Not frequent in NF1 and Noonan syndrome; some in CFC
Gait

- Stride, cadence, velocity
Other

• clubfeet requiring surgery
• other joint contractures (elbow, knees, etc.)
  • other joint dislocations
  • hypotonia
Osteopenia/Osteoporosis

**NF1 and Noonan**
Multiple studies show osteopenia/osteoporosis

**Costello:**
Two papers show anecdotal osteopenia in small groups
Each syndrome increased compared to controls ($p<0.0001$)
Orthopedic Overlap

- Scoliosis
- Osteopenia
- Bone cysts
- Vertical talus
- Pectus
- Short stature
- Hip dysplasia
- Heelcord contractures
- Pes planus

NF1

CFC

LEOPARD

Legius

Noonan

Costello
Bone Abnormal in RASopathies
What about Muscle?
Muscle Biopsies (Tidyman et al., 2011)

excessive variability of muscle fiber size and type II fiber predominance

In vitro studies showed that mutations that cause Costello and CFC syndrome (HRAS, BRAF, MEK1) inhibit myoblast differentiation
Strength

- Force applied by hand grip
- Measured by dynamometer
Physical Activity

Could increased physical activity improve the musculoskeletal findings?
Have you ever heard this?

“Stay fit and eat right.”

Need tools and tips catered for a child’s skill sets, capabilities, and health needs.
Average MET/week

Physical Activity

Could increased physical activity improve the musculoskeletal findings?

LESSONS LEARNED FROM NF1
(BOT-2)

Widely used Motor Proficiency Test (quantitative)

Game-like tasks (balance on one leg, bouncing a ball, cutting out a circle, etc.) – 8 subtests

Clinical validity studies on developmental coordination disorders

Valid for ages 4-21

1 hour to complete
BOT-2 (Eight Subtests - Examples)

Upper-limb coordination
(e.g. throwing ball at target)

Balance
(e.g. walking forward line)

Strength (e.g. standing wall sit)

running speed and agility
(e.g. one-legged side hop)
Total and Composite Scores (from 8 subtests)

Total motor composite: (z-score -1.62, p<0.5)
- 22/26 well-below or below ave.; none above average

Fine manual control: (z-score -0.93)
Manual coordination: (z-score -0.95)
Body coordination: (z-score -1.37)
Strength and agility: (z-score -1.48)*

*Regression analysis of relationship between motor area composite scores and total motor composite score showed that 67% of the variance accounted for by the strength and agility composite score.

*Johnson et al., Pediatric Physical Therapy 2010
Impact of Loading on Skeleton

- Studies in adult women show that weight bearing and resistance exercises increased BMD of the spine (Bonaiuti et al., 2002).

- Will targeted physical therapies improve BMD and overall health in the Rasopathies?
What Exercise Program is Right?

- Currently investigating the effects of a jumping program on muscle coordination, strength and bone quality in NF1

(study in progress)
Mean change in Force
After 10 weeks of twice a week 45 minute Plyometric exercise

Joint Motion Tested

- Shoulder
- Elbow
- Wrist
- Knee
- Ankle
- Hip

Intervention: N=3
Control: N=4
Activity Level

Utilization of Strengths

- Outgoing and sociable personality
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Conclusions

• Individuals with Costello syndrome should be evaluated by an orthopedist.

• Evaluation by an experienced physical therapist recommended.

• Encourage physical exercise regimens

• Identify weaknesses and strengths to develop most effective programs.

• Potential impact on multiple organ systems (e.g. skeletal - scoliosis, bone density)
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