Fractures and Osteopenia in Rett Syndrome

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Presentation Outline

- Fracture risk & Measures of bone strength in RS
- Contributors to decreased bone strength
- Optimizing bone strength acquisition
- Bone in the Aussie-Rett study
Fracture risk in RS

- 1/3 (35%) with RS in Australia had at least 1 fracture
- Estimated 40% would sustain a fracture by 15 years
  Leonard H et al, Dev Med Child Neurol 1999 41:323-8
- BUT - Normative Australian data suggests 45% risk of fracture in healthy children <18 years
  Sherker et al et al, MJA 2004
- Increased risk if
  - risk takers
  - decreased Ca intake
  - immobilization
  Goulding A et al, J Ped 2005
Bone Strength

Bone Mineral Material Properties

60-80% Bone Strength

Bone Geometry

Material Properties

Trabecular Microarchitecture
X-ray studies

Hand and foot X-rays of 94 RS girls + age controls
- Short 4\textsuperscript{th} metatarsal and ulna in > 50% > 5 years
- Short 4\textsuperscript{th} metacarpal 2x as common in RS cases as controls
- Earlier maturation vs controls

Geometry via Radiogrammetry of 2\textsuperscript{nd} metacarpal
- 80% had cortical thinning, ¼ severe
- Mean cortical thickness -1.94SDs RS vs -0.38 controls (p<0.001)
- Cortical thinning
  - Related to anticonvulsant use
  - Not related to calcium intake

Leonard H et al, Dev Med Child Neurol 1999; 41:323-8
Densitometry & Material properties

- 82 girls (2-21y) versus age controls
- DXA (radius), US (calcaneus, phalanges)
- Didn’t adjust for size
- RS girls
  - Decreased aBMD proximal and distal radius
  - Decreased SOS, BUA and stiffness at calcaneus
  - Ambulatory significantly greater DXA & US values
  - Anticonvulsants = lower values
  - 25 OH vitamin D levels < controls

Ceppolaro C et al, Calf Tiss Int; 2001 69: 259-62
Bone strength in RS - biopsy

- Bone histo-morphometry (iliac crest biopsy after tetracycline double labelling)
- 5 girls (9-14 years), at scoliosis surgery
  - Decreased bone volume
  - Normal or decreased formation (osteoid surface)
  - Decreased resorption (osteoclast surface & no.)

Budden SS & Guinness ME J Child Neurol 2003 18: 698-702
Contributors to decreased bone strength in RS

- Muscle strength
- Calcium intake
- Vitamin D
- Delayed puberty/ suppression of menstruation

With an increased propensity to fall
Muscle strength and bone

The muscle bone unit

\[ r^2 = 0.95 \]
\[ n = 322 \]

Courtesy Julie Briody, CHW
Vitamin D deficiency

- Diet (fatty fish, eggs, liver, fortified margarine)
- Decreased sun exposure
- Sunscreen
- Anti-epileptic drugs
Optimize bone strength acquisition

Address risk factors in everyone

- **Muscle strength**
  - Maximize weight-bearing activity
  - If can’t, physio / hydrotherapy

- **Calcium intake**
  - Meet RDI
  - If can’t, calcium supplements (1200mg/ day)

- In delayed puberty, consider sex hormone therapy

- For menstrual suppression, consider OCP rather than provera
Optimize bone strength acquisition

Vitamin D

- Adequate sun exposure without sunscreen, daily
  - Face, hands and arms for 6-8 minutes (summer), 30 mins (winter)
    Henderson et al 1997 J Child Neurol 12:443-7
- Diet rich in vitamin D
- Consider supplements if inadequate/ high risk
  - 400-800 IU daily
- Screening in high risk (anti-epileptics, dark skin, covered, malabsorption)
  - 25 hydroxy vitamin D, calcium, phosphate, alkaline phosphatase, PTH
- Treatment, then supplements, in deficient
  - 3000-5000 IU daily for 3+ months, with monitoring

Working group of ANZBMS MJA 2005 182: 281-5
Assess bone strength in girls with pathological/recurrent fracture or bone pain

- **Densitometry (DXA scan)**
  - Dependent on weight/height/puberty
  - Needs expert scanning & interpretation

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<th>Age (years)</th>
<th>BMD (g/cm²)</th>
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<td>30</td>
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Females

Males

Courtesy Julie Briody, CHW
Bisphosphononates: structure

P-C-P group is Essential for
• Binding to hydroxyapatite
• Biological activity

When R1 is an OH, binding to hydroxyapatite is enhanced

R2 side chain determines potency
Bisphosphonates: action

intracellular uptake of bisphosphonate by osteoclasts during resorption

loss of resorptive function

apoptosis

Formation >> Resorption = net >>
Bisphosphonates: sequelae

Mainly with IVI, not oral therapy - from studies in OI

- “flu-like” illness in 83%
  - Fever, joint and bone pain, vomiting
  - Mainly with 1st dose
  - Relieved by use of brufen

- Transiently low calcium
  - Worse if low calcium / vitamin D deficient

- Uveitis
- ? Nephrocalcinosis
- ? Teratogenic risk – long half life, crosses placenta
Bisphosphonate therapy

- Needs careful investigation, consideration then management by endocrinologist/bone physician
- Only with fracture/bone pain
- No outcome study results in RS
- Better results with
  - IVI vs oral
  - Pre- and pubertal children, rather than post-pubertal
  - High bone turnover states
- If considered, should be done in a study trial
Aussie-Rett study

- Multi-centre, across Australia
- All RS children and young adults, 2005 & 2007
- Fracture history
  - number/ site(s)/ age/ mechanism of injury
- Bone mass and geometry (DXA)
- Contributing variables
  - Genotype
  - Family history of osteoporosis (questionnaire)
  - Medical history and medications (questionnaire)
  - Muscle strength (mobility assessed by video)
  - Muscle size (DXA)
  - Ca intake (food frequency questionnaire)
  - Vitamin D (Sun exposure and sunscreen use-questionnaire)
  - Height/ Weight and pubertal status (Tanner stage)
  - Vitamin D status (bloods) and turnover if low DXA, in 2007