Osteoporosis/ Osteopenia in RDEB- what’s new?

4th Conference EB-CLINET
Dr Anna Martinez
September 27th 2017
Outline

• Review of the literature
• Bone basics
• Risk factors for osteopenia in EB
• What’s new
  • Retrospective study of children with RDEB at GOSH
  • Current status of bone health
• What’s next
Current key literature bone health

- Francis Palisson group 2002
  - 7 children generalised EB
  - 3 had reduced BMD, low Vit D and severe limited mobility
- Anna Martinez group 2006
  - 39 children
  - All RDEB and JEB low BMD compared to matched controls
  - Correlation with inactivity not with Vit D
Current key literature bone health

• Anna Bruckner group 2011.
  • prospective study 24 children 2 centres
  • 20 RDEB had low aBMD
  • mobility was associated with low aBMD but not Vit D levels

• Tivoli in Milan 2017.
  • 20 children all 4 types of EB (10 RDEB)
  • Reported an association with Birmingham EB severity score & Vit D status with low BMD
3 chances to get our bone banked
Two Types of bone

• Cortical
  • dense outer part 80% weight of bone

• Trabecular bone
  • end of long bones
  • inside vertebral bodies
    • metabolically active bone
Long Bones

[Diagram of Long Bones with labels: Endochondral Ossification, Metaphyseal Inwaisting, Periosteal Apposition, Bone Remodelling]
Vertebral Bodies
Bone remodelling cycle
Osteocytes

• Osteocytes make up 90% of the body's bone cells in a connecting network.

• This network feeds back mechanical strain to the osteoblasts & osteoclasts.
Osteocytes

• Produce 2 essential cytokines
  • nuclear factor kappa B (NF-kB) ligand (RANKL)
  • macrophage colony-stimulating factor (M-CSF)

• Cytokines critical regulation osteoclast activity
Bone strength dependent is on

- Mobility - bone loading
- Good nutrition - calcium and vit D
- Attainment of puberty
- Healthy and adequate numbers of bone cells
Pubertal delay in EB patients

• Central delay as in other chronic inflammatory diseases

• Reduction GnRH
  • reduction FSH/LH
IL-6 → GnRH → Hypothalamus → Pituitary → LH, FSH → Secondary hypogonadism
Puberty in EB patients

• Skeletal mass approximately doubles during puberty
Abnormal bone regulation

• Inflammation
  • activation of inflammatory cytokines
    • interleukins 1 & 6
    • TNFα
  • RANKL
Abnormal bone regulation

• **Reduction mesenchymal stromal cells**
  • Dr Tamai mentioned on Monday
  • Osteoblasts originate from these cells
  • This is likely to have impact on bone building potential in patients with EB
Bone remodelling cycle
Retrospective comparison of bone health in children with RDEB

• Jan 2000-Aug 2007
• 40 patients with RDEB aged 7-8 and 15-18 years
• 20 in each group
Primary outcome measures

- vertebral fractures
- scoliosis
- pubertal delay
- lumbar spine aerial Bone Mineral Density (aBMD)
- age adjusted Z score (Z-score)
Lumbar areal Bone Mineral Density
Results 7-8 year old RDEB group 2007

- 36% had vertebral fractures
- 11% had scoliosis
Results 15-16 yr old RDEB group 2007

• 40% had vertebral fractures
• 30% had scoliosis
• 84% of these children had pubertal delay.
Pubertal delay definition

• Girls:
  • no breast development by 13 years in girl
  • no Menarche by 16 years

• Boys
  • testicular volume <4mls before 14 years
Results

• There was a highly significant decrease in BMD Z score (p<0.0001) with age
Abnormal BMD scores are not a fracture predictor

• Surprisingly patients with fractures did not have significantly different BMD Z-scores from those without (P=ns, t-test).
Results

- Fractures present silently in vast majority cases
- Youngest child female age 5.75 years
Results in 2017 age 7-8 yrs.

• 6 children
  • 1 fracture
Age 8 girl

- 8 year old girl
- Fully mobile
- Normal biochemistry
- Presented July 2017 sudden onset back pain whilst in shower
- Last screen X-rays April 2017 normal
Age 8 girl

- Loss of 25% vertebral body height L2-L5
- Depression endplates
- Boxes collapsed
Results 15-16 yr old RDEB group 2017

- 3 children
  - no fractures
  - all reached puberty
Proposed screening & monitoring of bone health in RDEB

• Lateral spine X-ray annually from age 5 years
• DEXA
  • baseline age around puberty
  • before starting bisphosphonates
  • annually for monitoring treatment
Treatment of fractures

- Use bisphosphonates well tolerated
- Intravenous zoledronic acid
  - short infusion
  - 6 monthly
  - highly effective OI
We are making a difference

• In many ways
• Better overall care
How can we prevent fractures?
How can we prevent fractures?

• Optimize
  • nutrition
  • wound care
  • mobility
Pubertal attainment crucial

• Endocrinologist
• Psychologist
The future

• Good longitudinal studies of bone health
• Trials of non pharmacological interventions such as vibration platforms
• Pubertal attainment is critical to bank more bone mass and reduce fracture risk
• Consider new medicines for osteoporosis
  • Denosumab anti-RANKL
Acknowledgements

- Dr Moira Cheung
- All patients & team at GOSH