Endocrinology: Bone Issues and their Treatment in Rett Syndrome

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My History with Rett Syndrome....





Brain Dev. 1985;7(3):276-80.

Rett syndrome: Swedish approach to analysis of prevalence and cause.

Hagberg B

The prevalence of the Rett syndrome was found to be approximately 1:15,000 in south-western Sweden. About 40 cases have now been traced in this country, the majority during the last 2 yrs. Experiences of over 20 yrs in efforts to obtain information on the etiology and pathogenesis are summarized. The neurobiological approach used in Gothenburg today to try to reveal the origin is described. A plea is made for developmental screening of deteriorating hand skill as a tool for early identification of potential cases of the Rett syndrome.



Brain Dev. 1985;7(3):297-9.

Rett syndrome: a case report from an audiovisual program.

Holm VA

A case report of a 13-yr-6-mo-old girl with the Rett syndrome is provided from an audiovisual program featuring home movies taken from 2 mos of age and onward. The patient shows the following symptoms not previously emphasized in the Rett syndrome: deceleration of head growth (rather than acquired microcephaly), fall-off in linear growth in infancy, early hypotonia, precocious puberty and respiratory alkalosis. Except for the precocious puberty, a second, 35-mo-old, patient has followed the same clinical course with similar laboratory findings.

Am J Med Genet Suppl. 1986;1:119-26.

Physical growth and development in patients with Rett syndrome.

Holm VA

Linear growth and sexual development was assessed in 21 girls who fulfilled the clinical criteria of Rett syndrome. Ten (48%) showed growth retardation with length or height below the 5th centile and an additional 8 (38%) had shifted their linear growth downward sometime during the first years of life. All the girls had ageappropriate sexual development with menarche in 6 at a mean age of 11 2/12 years. Early deceleration of linear growth, growth retardation and normal sexual development appear to be useful markers in the clinical definition of Rett syndrome.

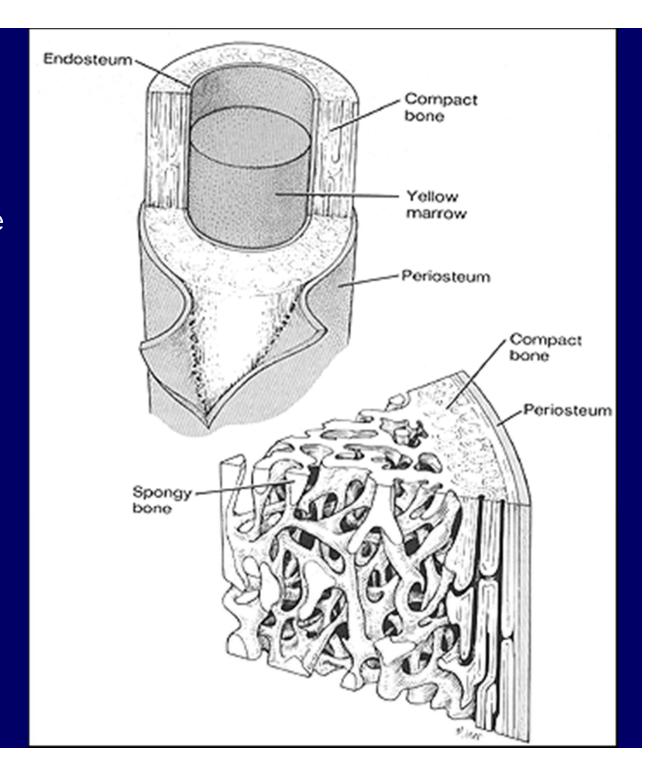
Overview

- The skeleton and mineral metabolism
- Evaluating children at risk for a low bone density
- Bone density in Rett syndrome
- Treatment of low bone density

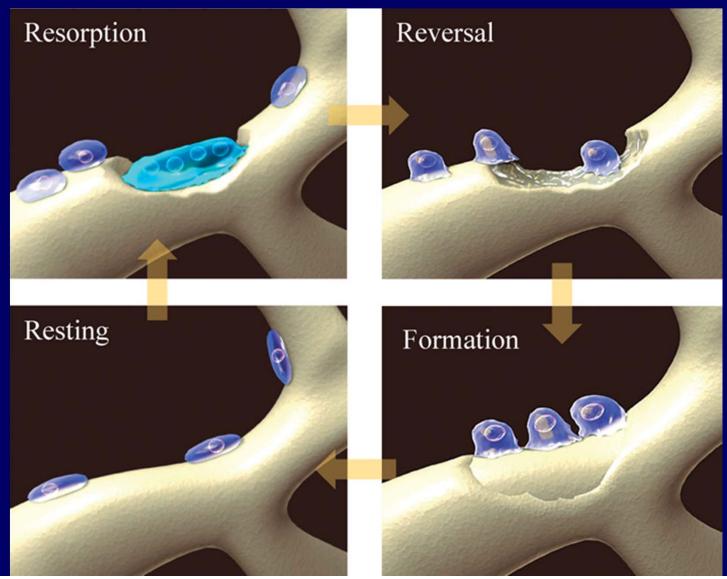
Mineral metabolism and skeletal physiology

Bone

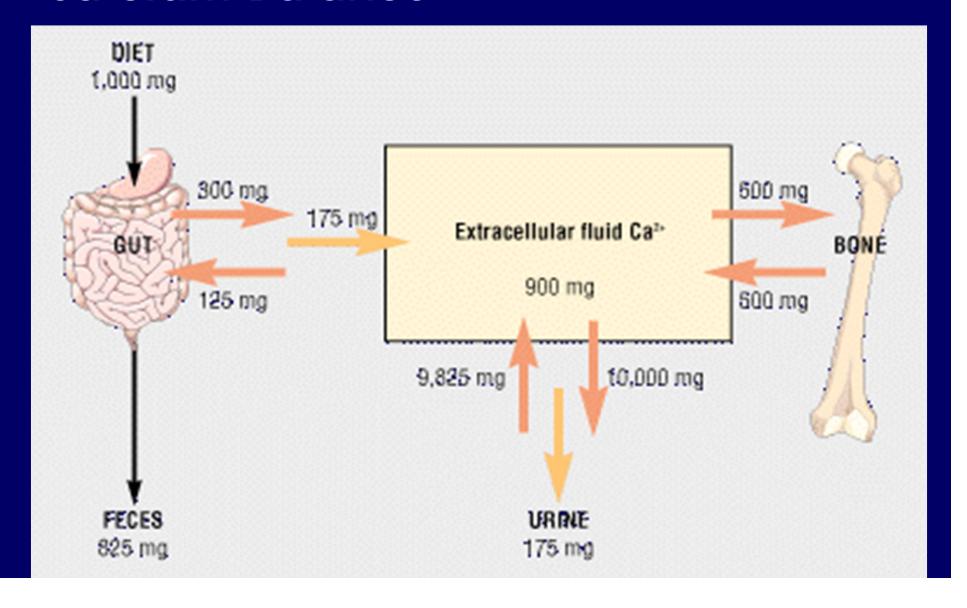
- Mineralized tissue
- Bone marrow
- Nerves
- Blood vessels
- Cartilage



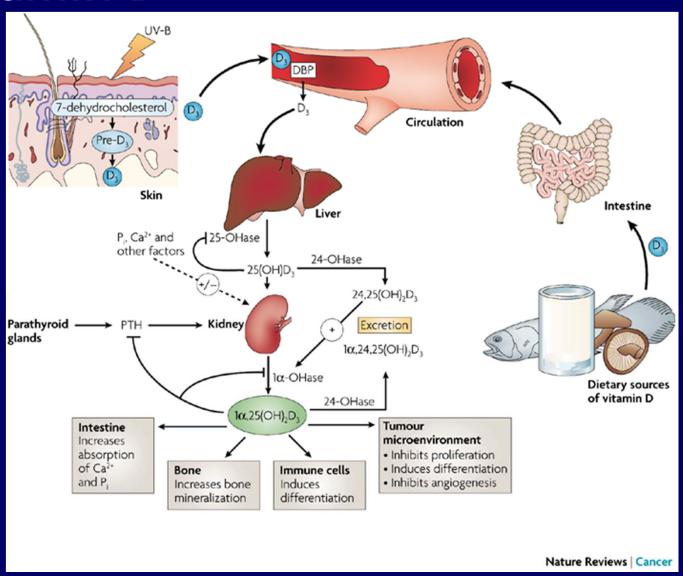
Bone turnover



Calcium Balance



Vitamin D



Daily recommended intake of calcium for age

| Calcium | Recommended Daily Allowance | | | | |
|-------------------------------------|-----------------------------|--|--|--|--|
| Infants | 350 - 550 mg | | | | |
| Children 1-10 years | 800mg | | | | |
| Teenagers | 1200mg | | | | |
| Pregnant and Breastfeeding Women | 1300 – 1500mg | | | | |
| Adults | 800 – 1000mg | | | | |
| Post Menopausal Women | 1300 - 1500mg | | | | |

http://www.dairyfreecookingforkids.com/Dairyfreecookingforkids.html

Translated into glasses of milk per day

8 ounces of milk has 300 mg calcium



Calcium Content of Some Foods

Milk products

- Milkshake 10 oz 400 mg
- Yogurt 1 c350 mg
- Ricotta 1/2 c 330 mg
- Milk 1 c300 mg
- Cheese 1 oz 200 mg

Meat Group

- Salmon 3 oz 170 mg
- Sardines 3 oz 370 mg

Vegetable Group

Greens 1/2 c90-120 mg

Grains

Pancakes 4"120 mg

"Fast foods"

Pizza Hut's supreme personal pan pizza

520 mg

Mac/cheese 1 c350 mg

Big Mac250 mg

Cheeseburger180 mg

Taco Bell taco80 mg

Recommended serum vitamin D (25-hydroxyvitamin D) levels

| nmol/L | ng/mL | Health status |
|-----------|--------------|---|
| <30 | <12 | Associated with vitamin D deficiency, leading to rickets in infants and children and osteomalacia in adults |
| 30–50 | 12–20 | Generally considered inadequate for bone and overall health in healthy individuals |
| ≥50 | ≥20 | Generally considered adequate for bone and overall health in healthy individuals |
| >125 | >50 | Emerging evidence links potential adverse effects to such high levels, particularly >150 nmol/L (>60 ng/mL) |
| Office of | dietary supp | lements, NIH |

Vitamin D (25-hydroxyvitamin D) levels in NHANES 2000-2004

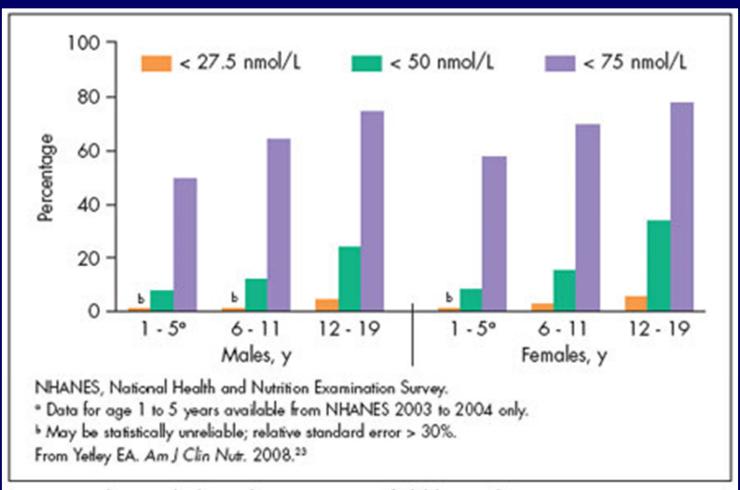


Figure 2 – This graph shows the percentages of children in the NHANES 2000-2004 studies, by age and sex, whose 25-hydroxyvitamin D_3 levels fell into each of 3 ranges: < 27.5 nmol/L, < 50 nmol/L, and < 75 nmol/L.

Recommended Vitamin D Dietary Allowances (RDAs)

| Age | Male | Female | Pregnancy | Lactation |
|--------------|--------|--------|-----------|-----------|
| 0–12 months* | 400 IU | 400 IU | | |
| 1–13 years | 600 IU | 600 IU | | |
| 14–18 years | 600 IU | 600 IU | 600 IU | 600 IU |
| 19–50 years | 600 IU | 600 IU | 600 IU | 600 IU |
| 51–70 years | 600 IU | 600 IU | | |
| >70 years | 800 IU | 800 IU | | |

Evaluating children at risk for a low bone density

Dual Energy X-Ray Absorptiometry (DXA) Scan

- Determine bone mineral density (BMD)
- Used extensively in post-menopausal women
- Now being used more and more in children
 - Standards for children available
- Safe, easy, non-threatening for children
 - Low radiation 1/10th of a chest x-ray

DXA Spine and Hip Scans





Children's Hospital 300 Longwood Ave.

Boston, MA 02115



Sex: Male Ethnicity: Pediatric

Height: Weight: Age: 10

Referring Physician: Holm, Ingrid

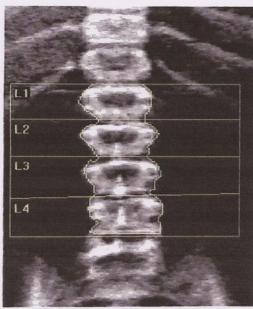


Image not for diagnostic use 116 x 92

Total Age

Scan Information:

Scan Date: February 18, 2010 ID: A0218100B

Scan Type: f Lumbar Spine

Analysis: February 18, 2010 14:00 Version 12.3

Lumbar Spine (auto low density)

Operator:

yc Discovery A (S/N 81408) Model:

Comment: 3rd f/u

DXA Results Summary:

| Region | Area (cm²) | BMC | BMD (g/cm²) | T - Score | PR (%) | Z - Score | AM (%) |
|--------|---------------|-------|----------------|--------------|--------|--------------|-----------|
| LI | 6.82 | 3.23 | 0.474 | -4.7 | 46 | -1.2 | 81 |
| L2 | 7.12 | 4.06 | 0.570 | -4.0 | 51 | -0.8 | 90 |
| L3 | 8.39 | 5.21 | 0.621 | -3.8 | 55 | -0.4 | 95 |
| L4 | 7.82 | 5.24 | 0.671 | -3.3 | 61 | 0.3 | 104 |
| Total | 30.14 | 17.73 | 0.588 | -4.3 | 54 | -0.5 | 93 |

Total BMD CV 1.0%

Physician's Comment:

Children's Hospital 300 Longwood Ave.

Boston, MA 02115

Telephone: 617-355-7541

Sex: Male Ethnicity: Pediatric Height: Weight: Age: 10

Referring Physician: Holm, Ingrid

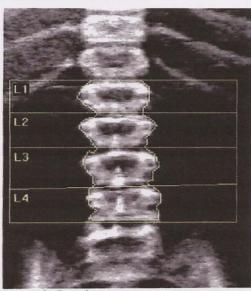


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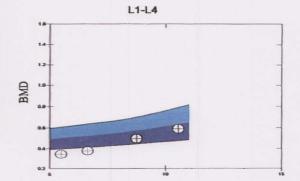
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Comment: 3rd f/u



Reference curve and scores matched to Pediatric Male

Source: 2004 ASBMR Abstract #SU112

DXA Results Summary: L1-L4

| Scan Date | Age | BMD (g/cm²) | T - Score | BMD Change | | |
|------------|-----|----------------|--------------|-------------------------|--|--|
| | | | | vs Baseline vs Previous | | |
| 02/18/2010 | 10 | 0.588 | -4.3 | (71.5%* (18.9%* | | |
| 05/02/2008 | 8 | 0.495 | -5.1 | / 44.3%* / 31.7%* | | |
| 03/23/2006 | 6 | 0.376 | -6.1 | 9.6%* 9.6%* | | |
| 01/28/2005 | 5 | 0.343 | -6.4 | | | |

Total BMD CV 1.0%

^{*} Denotes significant change at the 95% confidence level.

Evaluating Children With a Low BMD

Look for causes contributing to the low BMD

- Disorders of vitamin D and calcium intake and/or metabolism
 - Malabsorption
- Chronic diseases
- Medications steroids, etc.
- Hormonal deficiencies
 - Thyroid disease
 - Hypogonadism
 - Growth hormone

Osteopenia in Rett Syndrome

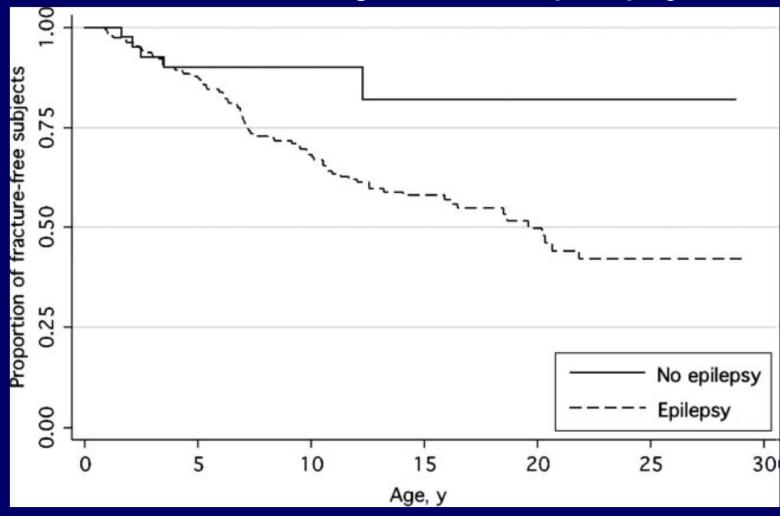
Girls with Rett Syndrome have a low bone mineral density

- Reduced bone size
- Lower BMD
- Low BMD associated with low-energy fractures

Factors contributing to the low BMD in Rett syndrome

- Narrow bones
- Decreased muscle mass, likely secondary to decreased mobility
- Lack of ambulation
- Anticonvulsant use
- Calcium and vitamin D
- May be effects of MECP2 directly on bone but still unclear

Kaplan-Meier survival estimates of time to first fracture in subjects with (n 192) and without (n 41) a diagnosis of epilepsy



Downs, et. al.,, Pediatrics 2008

Treating a low BMD in children

Not many options

Treatment options

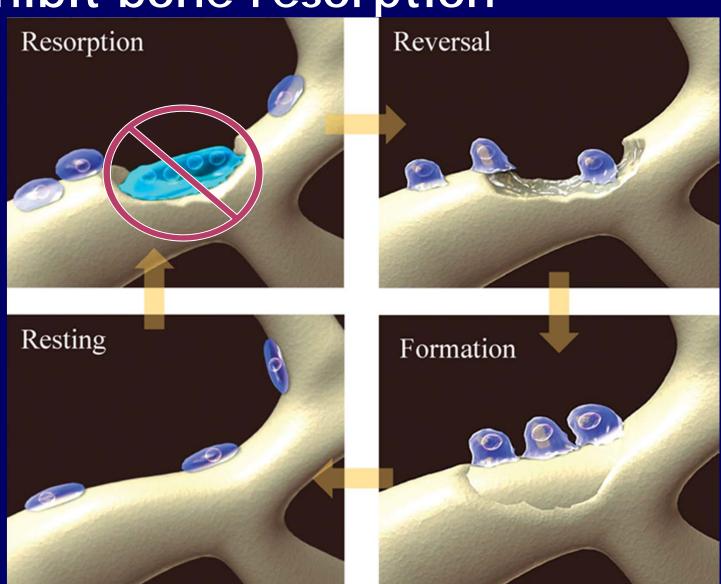
- Treat conditions contributing to the low BMD
 - Vitamin D, calcium, etc.
- Optimize physical activity
- Pharmacological therapies
 - Bisphosphonates
- Newer possibilities: Vibration therapy

Bisphosphonate Therapy for Pediatric Osteoporosis

Bisphosphonates

- A class of medications originally used to treat osteoporosis in post-menopausal women
- Inhibit bone resorption
- Bone retention 20-80%
 - What is not retained in bone is excreted in urine
 - Remains in the bone for a long time
 - ½-life in bone ~1 year

Inhibit bone resorption



Oral Bisphosphonates

- Preparations
 - Alendronate (Fosamax)
 - Daily or once a week
 - Risedronate (Actonel)
 - Daily or once a week or twice a month
 - Ibandronate (Boniva)
 - Daily or once a month
- Side effects
 - Gastrointestinal ulcers, esophagitis
 - Poor intestinal absorption
 - Rare severe bone, joint or musculoskeletal pain

Intravenous bisphosphonates

- Preparations
 - Pamidronate
 - 3 hour infusion every few months
 - Zoledronic Acid (Zometa)
 - Once-twice a year
- Common side effects
 - Hypocalcemia
 - Flu-like symptoms with the first dose only
- Rare complications
 - Osteonecrosis of the jaw
 - Most cases following high-dose administration in cancer patients
 - ~60% of cases preceded by a dental surgical procedure
 - Recommendations: bisphosphonate treatment should be postponed until after any dental work to eliminate potential sites of infection.
 - Severe bone, joint or musculoskeletal pain

Use of Bisphosphonates in Children

- Not FDA approved in children
- Not well-studied no long-term studies
 - Severe osteogenesis imperfecta
 - Cerebral palsy a few studies show improvements in BMD
- Oral medications are hard for children to take
- The longer the ½ life, the longer the medication stays in growing bone

Vibration therapy

 A few studies in cerebral palsy show potential for moderate effect on bone density



Summary

- Bone is dynamic
 - Requires vitamin D and calcium
- A low BMD is common in Rett syndrome
- Monitoring BMD by DXA is feasible in children and adults
- If the BMD is low, look for, and treat, secondary causes
- There is no good therapy for children with a low BMD, but bisphosphonates may be an option in children with multiple fractures
- New therapies may be on the horizon

Thanks mom!

