Newborn with Fractures

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Pediatric Endocrinology Fellow
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Chief Complaint

- 2-day-old F with prenatally dx’ed osteogenesis imperfecta (OI).
HPI

- Born via repeat C/S to a 30 yo G3P2 mother
- No delivery complications
- Pregnancy complications included incompetent cervix dx’ed at GA 28 wks
- Left femur fracture noted on prenatal U/S
- Genetic w/u revealed +frame shift mutation c/w OI type I
HPI cont’d

- Evaluated by ortho on DOL 1
- LLE XR showed a questionable lucency of the left tibia
- Splint applied to LLE
LLE XR
**ROS**

- General: + **good appetite.** – fever, fatigue
- Endocrine: + **adequate UOP, euglycemia**
- HEENT: – deformities
- Resp/CV: + stable on room air
- GI: – vomiting, diarrhea, constipation
- GU: – polyuria
- Skin: – rash, pallor, jaundice
- MSK: + **LLE fracture**
- Neuro: + **alert**
Further History

PMH/PSH:
- LLE fracture s/p splint placement

FH:
- Grey sclera, h/o fractures- father
- Otherwise noncontributory

SH:
- Will live at home with parents and younger sister, who is healthy.
Physical Exam

- Vitals: T 36.7, HR 130, RR 30, BP 81/51, Wt 3.5 kg (71%ile), length 51 cm (70%ile), HC 34.5 cm (60%ile)
- General: Alert, well-developed. No distress
- HEENT: Moist mucous membranes, no congestion, normal EOM, +gray conjunctiva
- Neck: Supple. Thyroid not palpable
- Pulm/CV: CTAB, nL air entry, RRR, 2+ distal pulses
- GI: S/ND/NT, +BS, no hepatosplenomegaly or masses
- GU: normal prepubertal female genitalia
- MSK: +LLE in splint. Other extremities with nL range of motion, no edema or deformities
- Neuro: +age appropriate reflexes, nL muscle tone
Labs

- 137 105 7
- Ca 9.5, phos 5.9, Mg 2.1
- 25-OH vit D 16
- NBS #1 negative
- Skeletal survey: Healed L femur fracture. No other evidence of acute or healing fractures.
Skeletal Survey
Clinical Objectives

- Review OI
- Discuss bisphosphonate tx
- Examine the effect of long-term pamidronate tx on height and weight
Review of OI

- Incidence: 1–2 per 20,000 live births
  - All races and gender affected equally
- Most cases = spontaneous mutation
  - If inherited, majority = AD pattern
- >250 molecular defects identified
- 80-90% have a mutation in **COL1A1** or **COL1A2** → defective polypeptide chains \( \alpha_1 \) and \( \alpha_2 \) (type I collagen)
# Sillence Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical Severity</th>
<th>Typical Features</th>
<th>Typically Associated Mutations*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Mild non-deforming osteogenesis imperfecta</td>
<td>Normal height or mild short stature; blue sclera; no dentinogenesis imperfecta</td>
<td>Premature stop codon in COL1A1</td>
</tr>
<tr>
<td>II</td>
<td>Prenatal lethal</td>
<td>Multiple rib and long-bone fractures at birth; pronounced deformities; broad long bones; low density of skull bones on radiographs; dark sclera</td>
<td>Glycine substitutions in COL1A1 or COL1A2</td>
</tr>
<tr>
<td>III</td>
<td>Severely deforming</td>
<td>Very short; triangular face; severe scoliosis; grayish sclera; dentinogenesis imperfecta</td>
<td>Glycine substitutions in COL1A1 or COL1A2</td>
</tr>
<tr>
<td>IV</td>
<td>Moderately deforming</td>
<td>Moderately short; mild to moderate scoliosis; grayish or white sclera; dentinogenesis imperfecta</td>
<td>Glycine substitutions in COL1A1 or COL1A2</td>
</tr>
<tr>
<td>V</td>
<td>Moderately deforming</td>
<td>Mild to moderate short stature; dislocation of radial head; mineralized interosseous membrane; hyperplastic callus; white sclera; no dentinogenesis imperfecta</td>
<td>Unknown</td>
</tr>
<tr>
<td>VI</td>
<td>Moderately to severely deforming</td>
<td>Moderately short; scoliosis; accumulation of osteoid in bone tissue; fish scale pattern of bone of lamellation; white sclera; no dentinogenesis imperfecta</td>
<td>Unknown</td>
</tr>
<tr>
<td>VII</td>
<td>Moderately deforming</td>
<td>Mild short stature; short humeri and femora; coxa vara; white sclera; no dentinogenesis imperfecta</td>
<td>Unknown</td>
</tr>
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</table>
Prospective study
- 29 children who received pamidronate x3 yrs
  - All were <2 yrs at time of tx initiation
  - Included OI types I, III, and IV

- 101 treated children
  - All were <18 yrs at time of tx initiation
  - Almost exclusive to children with severe OI
Bisphosphonates- Background

- Structure is based on pyrophosphate, a naturally occurring substance known to inhibit bone metabolism
- Newest = 3rd-generation (e.g. risedronate)
  - Pamidronate and alendronate = 2nd-generation
- Inhibit farnesyl-pyrophosphate synthase
  - required for isoprenylation of intracellular proteins
- **Prevents attachment of lipids to proteins** that are tethered to cell membrane of osteoclasts → impaired function
  → **slowed bone resorption/remodeling**
Bisphosphonates - Benefits

- ↓↓ bone pain within few wks
- ↑ muscle strength, ↑ gross motor skills
- ↑ mobility in >= 50% of pts
- Faster rate of vertebral BMD ↑
- ↓ in long-bone fractures in <= 65% of pts
- Improved fracture healing
- Possible ↑ in mass of long-bone diaphyses
- May ↑ cortical thickness
  - no detectable effect on trabecular thickness
Bisphosphonates - Side Effects

- Few serious short-term SEs reported
  - Generally mild and reversible
- Most common = fever and body aches 12-36 hrs after 1st infusion
- Hypocalcemia, rapid weight gain, uveitis
- ↓ in respiratory function
  - In neonates with preexisting resp compromise
- ↓↓ bone turnover, ↑ mineralized growth plate material in secondary bone
Bisphosphonates - When & How

- Children with moderate to severe forms of OI
  - >2 fractures/yr, vertebral compression fracture, or long-bone deformities

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Dosage</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>&lt;2.0</td>
<td>0.5 mg/kg per day for 3 days</td>
<td>Every 2 months</td>
</tr>
<tr>
<td>2.0–3.0</td>
<td>0.75 mg/kg per day for 3 days</td>
<td>Every 3 months</td>
</tr>
<tr>
<td>&gt;3.0</td>
<td>1.0 mg/kg per day for 3 days;</td>
<td>Every 4 months</td>
</tr>
<tr>
<td></td>
<td>maximum dose 60 mg/day</td>
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Clinical Objectives

- Review OI
- Discuss bisphosphonate tx
- Examine the effect of long-term pamidronate treatment on height and weight
Height


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<tr>
<th></th>
<th>N</th>
<th>At Start of Therapy</th>
<th>After 4 Years of Therapy</th>
<th>P</th>
</tr>
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<tr>
<td>Height</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OI-I</td>
<td>12</td>
<td>100 ± 6</td>
<td>105 ± 7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>OI-III</td>
<td>14</td>
<td>99 ± 12</td>
<td>111 ± 14</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>OI-IV</td>
<td>15</td>
<td>102 ± 12</td>
<td>112 ± 11</td>
<td>&lt;.001</td>
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Weight


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<tr>
<td>OI-I</td>
<td>12</td>
<td>100 ± 15</td>
<td>112 ± 27</td>
</tr>
<tr>
<td>OI-III</td>
<td>18</td>
<td>114 ± 51</td>
<td>126 ± 59</td>
</tr>
<tr>
<td>OI-IV</td>
<td>17</td>
<td>96 ± 21</td>
<td>104 ± 23</td>
</tr>
</tbody>
</table>
Recs for our Patient

- Vitamin D supplementation
- Follow-up at the OI clinic at Shriner’s
- Tx will likely consist of maintaining a healthy diet and physical therapy
- Scoliosis screen Q1 yr after 6 yrs of age
- Hearing test Q3 yrs after 1 yr of age
Summary

- OI is a genetic disorder of ↑ bone fragility and ↓ bone mass
  - 80-90% due to mutation in COL1A1 or COL1A2
  - Type 1 = most common and mildest form
- Bisphosphonates are the mainstay for medical tx of moderate-severe phenotypes
  - ↓ bone remodeling, ↑ strength and ↑ mobility
  - Research in children (esp infants) is limited
- Tx for mild OI (type 1) includes healthy diet, PT/exercise, scoliosis and hearing screens
References