Osteogenesis
Imperfecta

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Definition

- Genetic disorder of reduced bone mass and bone fragility

- Variable extra-skeletal features:
  - Blue sclerae
  - Dentinogenesis imperfecta
  - Hyperlaxity
  - Hearing impairment
Diagnosis

- Incidence 2-4: 10,000
- Constellation of clinical features
- Family history
- Special tests seldom required:
  - Genetic analysis
  - Cultured fibroblast procollagen analysis
- Variable severity and prognosis therefore classifying groups is useful
Classification

- Sillence et al (1979):
  - 4 clinical subtypes based on clinical features
  - 3 additional subtypes based on clinical and histological features
- Key feature is bone fragility
- Other disorders exist with bone fragility but these are separate entities
  - Different gene and protein defects
<table>
<thead>
<tr>
<th>Type</th>
<th>Severity</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild</td>
<td>Blue sclerae, mild short stature</td>
</tr>
<tr>
<td>2</td>
<td>Lethal</td>
<td>Multiple fractures at birth, dark sclerae</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
<td>Short stature, grey sclerae (white later), progressive deformity, dentinogenesis imperfecta</td>
</tr>
<tr>
<td>4</td>
<td>Moderate</td>
<td>White sclerae, short stature</td>
</tr>
<tr>
<td>5</td>
<td>Moderate</td>
<td>Ossified interosseous membrane, white sclerae, hyperplastic callus</td>
</tr>
<tr>
<td>6</td>
<td>Moderate / Severe</td>
<td>White sclerae, ↑osteoid, “fish scale” lamellation</td>
</tr>
<tr>
<td>7</td>
<td>Moderate</td>
<td>Rhizomelia, coxa vara, white sclerae</td>
</tr>
</tbody>
</table>
Classification

- Severity of bone fragility (increasing):
  - 1 < 4, 5, 6, 7 < 3 < 2
- Types 1 and 4:
  - A = no dentinogenesis imperfecta
  - B = dentinogenesis imperfecta
- Type 2: Death due to respiratory failure
- Type 7: Isolated to Quebec
- Type 3: Most commonly treated by orthopaedic surgeons
Pathogenesis

- OI subtypes are clinical phenotypes
- Genotype / phenotype correlation weak
- Type 1 – 4 associated with mutations affecting COL1A1 and COL1A2 genes:
  - Autosomal dominant with variable expressivity
  - Code for Type 1 collagen (α1 and α2 chains)
- Type 7 separate gene locus:
  - Autosomal recessive
- Type 5, 6 unknown
Point mutation

Premature stop codon on COL1A1

Cell able to destroy abnormal transcription products (Nonsense mediated decay)

Net effect 50% reduction of (normal) \( \alpha_1 \) procollagen production

Mild phenotype (Type 1 – Classic OI)
Pathogenesis

Point mutation

Glycine residue substituted on $\alpha_1$ or $\alpha_2$ chain

Chains unable to bind normally

Abnormal collagen production

Severity of phenotype depends on chain affected, position of substitution and type of amino acid substituted
Pathological Changes

- Higher mineral density
- Increased turnover
- Reduced cortical thickness
- Reduced overall size
- Reduced size and number of trabeculae
- Abnormal lamellation
Medical:
- Bisphosphonates
  - Pulsed pamidronate IV, oral alendronate
  - Reduced fracture rate
  - Improved growth
  - Less bone pain
- Long term effects in children still unknown
  - Altered remodelling
  - Longitudinal growth
  - Influenza like reaction (first dose)
  - ?Reduced bone healing
- Not recommended for mild cases
Treatment

- **Surgical:**
  - Most fractures treated conservatively
  - Mobilise early
  - Surgery for deformity / pathological fracture / prophylaxis
    - Telescoping rods
    - ORIF needs to be meticulous
    - Nonunion rare but difficult to treat (“gap” nonunion)
Treatment

- General:
  - Physiotherapy
  - Protective orthotics at walking age
  - Rehabilitative measures
  - Lifestyle precautions
Future possibilities:

- Stem cell transplants (marrow stromal cells)
- Gene inactivation and substitution
- Parathyroid hormone
  - Osteosarcoma in rats
Prognosis

- Type 1 and 4:
  - Good, normal lifespan

- Type 3:
  - Often reduced lifespan
  - Frequent respiratory complications

- Type 2:
  - Perinatal death

- Fracture rates can decrease at maturity but may increase with pregnancy and always increase after menopause