



Osteogenesis Imperfecta

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Osteogenesis Imperfecta

- Definition & History
- Pathophysiology
- Clinical Presentation inc.
 - Testing
 - Diagnostic Imaging
 - Classification
- Differential Diagnosis & Non-Accidental Injury
- Treatment & Conclusion



Definition

A rare hereditary disease in which abnormal connective tissue development leads to fragile bones subject to fracture.





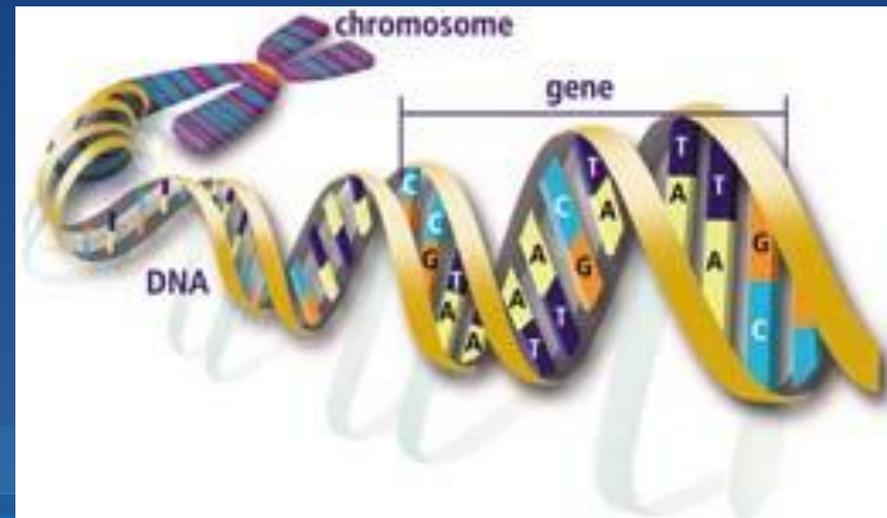
History

- **1788 – Olof Jakob Ekman**, described within his doctoral thesis and mentioned cases dating back to 1678
- **1831 – Edmund Axman**, described it in himself and 2 brothers
- **1833 – Johann Friedrich Georg Christian Martin Lobstein** dealt with it in adults
- **1850s – Willem Vrolik**, carried out further work on OI
- **1897 – Martin Benno Schmidt**, the idea that adult and newborn forms were the same.



Pathophysiology

- Disturbance in the synthesis of Type I collagen
- This is a predominant protein of the extracellular matrix of most tissues
- Defect causes osteoporosis, increasing the possibility of fracture
- Type I collagen is a major component of dentin, sclera, tendons & ligaments, blood vessels and skin = abnormalities





Pathophysiology

Mutations in 1 of 2 genes that encode the synthesis and/or structure of Type I collagen:

1. COL1A1 gene on chromosome 17
 2. COL1A2 gene on chromosome 7
- Results in abnormal or decreased production of normal collagen, or a combination leading to phenotypic expressions of OI.
 - Mild forms = decrease in production of collagen
 - Severe forms = abnormal production of collagen
 - Abnormalities may be dominantly inherited, or random mutation.



Clinical Presentation

Dependant upon 'Type' of OI

- Bone fragility
- Multiple fractures
- Bony deformities

- Blue Sclera



Figure—Three examples of blue sclerae.



Clinical Presentation

Other key features may include:

- Hearing Loss
- Dental abnormalities
- Joint laxity
- Abnormal skin texture – smooth & thin
- Easy bruising
- Ligamentous laxity & Hypermobility of joints
- Short stature
- Hyperplastic scars
- Abnormal temperature regulation





Testing

- Family History
- Clinical Examination
- Radiology
- Molecular & Biochemical Testing
 - may be indicated in certain cases
 - not wholly sensitive or specific; may be unclear
 - may take several months to become available due to the large size of the collagen 1 genes.
 - Negative results do not exclude a diagnosis as mutations are typically found in about 80-90% of cases of clinically unambiguous cases as stated by NHS Evidence (2005).



Diagnostic Imaging – Plain Film

- Primary imaging modality for diagnosis, supported by Greenspan (2004)
- Locally agreed protocol for imaging - skeletal survey inc. Long Bones, Skull, Chest, Pelvis & Thoracolumbar Spine
- Radiological features are related to the Type and severity, some may be seen in all subtypes
- Osteoporosis, deformities in bones and thinning of the cortices are consistently observed
- Bones are attenuated and gracile with trumpet-shaped appearances to the metaphysis



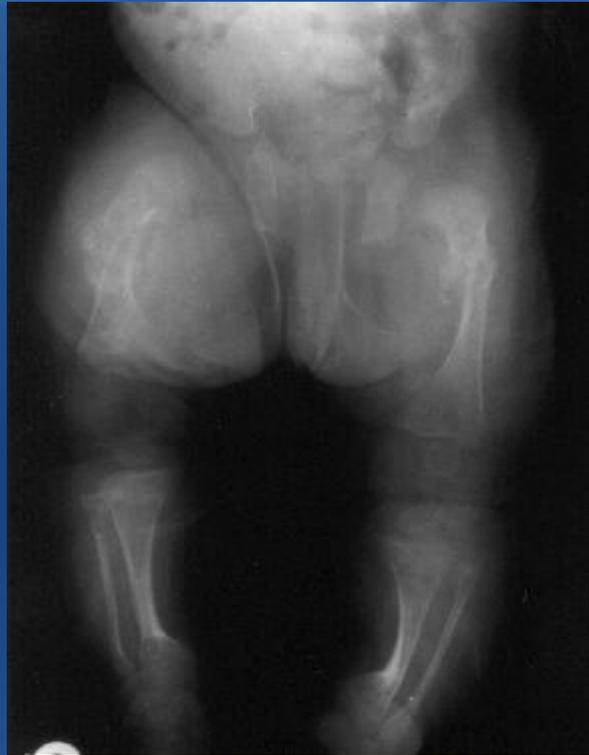
Diagnostic Imaging – Plain Film

- Other features include wormian bones seen in the skull, severe kyphoscoliosis in the spine +/- osteoporosis, ligamentous laxity, post-traumatic deformities
- Severe OI – metaphysis and epiphysis of long bones may show numerous scalloped radiolucent areas with sclerotic margins
- Referred to as “popcorn calcifications”
- Result from traumatic fragmentation of the growth plate
- Pelvis is always deformed
- Acetabular protrusion is a frequent finding



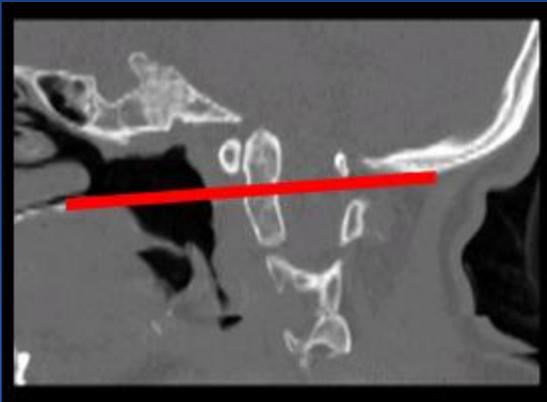
Diagnostic Imaging – Plain Film

<http://www.uhrad.com/pedsarc/peds016.htm>



Diagnostic Imaging – Computed Tomography

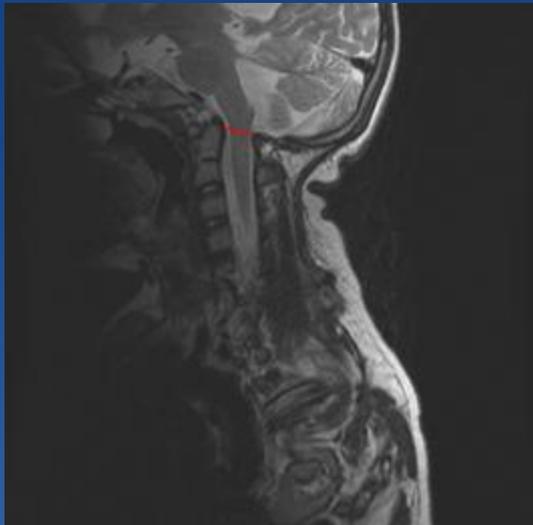
- Assess basilar impression
- Evaluate petrous bone for narrowing of the middle ear or otosclerosis
- Support bone mineral densitometry in DEXA



Kirpalani (2008) Sagittally reconstructed CT scan of the cervical spine in a 16-year-old female adolescent with Type IV OI. Image demonstrates mild basilar invagination, with the tip of the dens above the McGregor line (red).

Diagnostic Imaging – Magnetic Resonance Imaging

- Problem solving
- Image OI complication – particularly basilar impression
- CT detects basilar impression
- Able to detect spinal cord compression
- Basilar impression frequently associated with Type IV / IVB where neurological symptoms are increased



Kirpalani (2008) Midline sagittal T2-weighted MRI through the cervical spine in the same patient previous slide. Image demonstrates mild stenosis at the foramen magnum, caused by basilar invagination (effective width of foramen magnum denoted by red line).



Diagnostic Imaging – Ultrasound

- Most common dysplasias detected with US
- Involve Type II and are an incidental finding
- Diagnosis made reliably 17 weeks of gestation
- During 2nd trimester – decreased echoes from the calvarium with intracranial structures being easily seen, bowing of long bones, implying plastic deformities and fractures, decreased length of long bones and multiple rib fractures
- Compression of skull vault by US probe raises suspicion of skeletal dysplasia but not diagnostic for OI



Diagnostic Imaging – Ultrasound





Diagnostic Imaging – DEXA

Dual-Energy X-ray Absorptiometry

- Assess prognosis
- Monitor response to treatment
- May predict long term functional outcome
- Serial DEXA scanning routinely used as an objective assessment of response to bisphosphonate therapy
- Difficulties in interpretation, particularly if there are bone deformities in spine and / or hip.



Classification: Type I

- Most Common
- Autosomal-dominant inheritance
- Mild bone fragility
- Osteoporosis
- Sclera distinctly blue
- Hearing loss or impairment common
- Normal stature
- Wormian bones

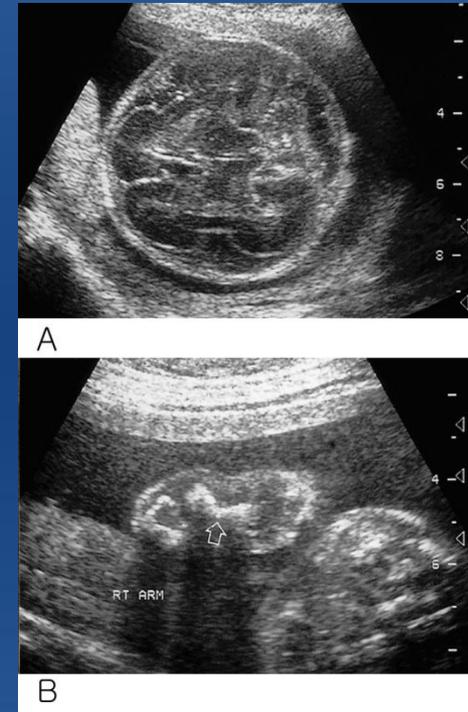
- Type IA – normal teeth
- Type IB – dentinogenesis imperfecta





Classification: Type II

- Fetal or perinatal
- Autosomal-dominant inheritance + new mutation
- Generalised osteoporosis, bone fragility, severe intrauterine growth retardation = death in fetal or perinatal period
- Those that survive, 80-90% die by 4 weeks
- Blue sclera, face has a triangle shape caused by soft craniofacial bones and a beaked nose
- Calvarium is large relative to face
- Limbs are short, broad and angulated





Classification: Type II



Poznanski, A. (2009)

OI Type II. Severe neonatal form.

This infant has the appearance of a short limb dwarf.

There is marked telescoping of bones particularly the femora.

Multiple healing fractures are seen. Some bones are bowed.



Classification: Type III

- Severe progressive form
- Rare autosomal-dominant inheritance with new mutations
- Bone fragility and osteopenia
- Lead with age to multiple fractures and severe deformity of long bones and spine
- Bone abnormalities are generally less severe than Type II – more severe than Types I or IV
- Normal Sclera – pale blue/grey at birth, colour changes through infancy and early childhood, normal by adolescence or adulthood
- Calvarium – large, thin, poorly ossified, wormian bones present.



Classification: Type III





Classification: Type IV

- Rare
- Inherited as an autosomal-dominant trait
- Osteoporosis, bone fragility and deformity present, but mild
- Sclera usually normal
- Low incidence of hearing impairment in comparison to Type I

Teh (2009) classifies Type IV into 2 further categories:

- Type IVA – absence of dentinogenesis imperfecta
- Type IVB – presence of dentinogenesis imperfecta



Classification

The table, by NHS Evidence (2005), below demonstrates these classifications and includes data of the prevalence of the disease per 100,000 and approximately how many fractures obtained in a lifetime.

Type	Prevalence /100,000	Lifetime Fractures (approx)
I	3 – 4	Few to 20's
II	1 – 2	LETHAL
III	1 – 2	➤100
IV	3 – 4	20 – 100



Differential Diagnosis

Osteoporosis – Multiple Fractures

- Juvenile Osteoporosis
- Steroid-induced osteoporosis
- Menkes (kinky-hair syndrome)
- Hypophosphatasia
- Temporary brittle-bone disease

Non-Accidental Injury



Differential Diagnosis & NAI

- Teh (2009) states Type IVA - likely to be confused with NAI
- Social circumstances & thorough clinical and imaging evaluation by specialists is essential
- Collagen analysis may be useful where there is uncertainty over supposed force of injury – insufficient to have caused fractures, when fractures occur in a protected environment, no external signs of abuse

OI and NAI can clinically present together

Specific features aid in diagnosis

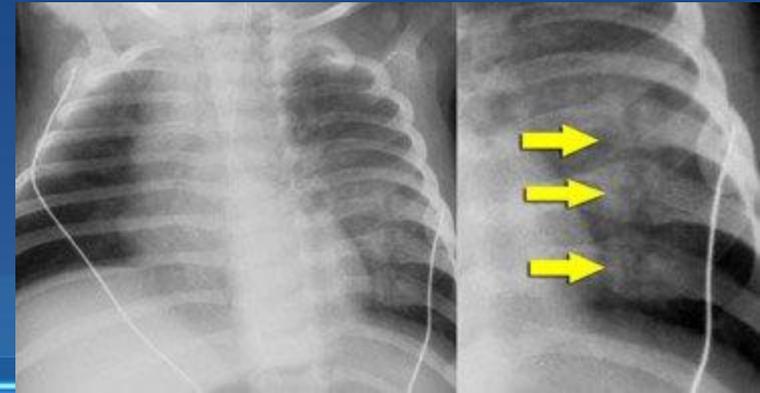


Differential Diagnosis & NAI

- Metaphyseal ‘corner’ fractures are a common radiological feature rarely seen in OI
- If this is present in OI – associated thin cortices and osteopenia
- Bucket-handle fractures and fractures of the sternum, scapula, and skull vault rare in OI
- Fractures of hands, outer ends of clavicles, spinal and posterior rib fractures strongly indicate NAI
- Children subjective to NAI – skeletal surveys show normal healing and remineralisation
- In OI – fractures continue to occur even when the child has been removed and placed in safeguarding protective custody



Differential Diagnosis & NAI





Treatment

- No specific treatment
- Correction of deformities and prevention of fractures
- Gorieux (1998) stated that cyclical IV bisphosphonates have been shown to reduce bone pain and fractures and to increase bone density and mobility with minimal side effects
- Kirpalani (2008) also supports this, IV pamidronate promoting bone growth, relieving chronic pain
- Surgical intervention for recurrent fractures or deformity
- Preferable to treat fractures with short-term immobilisation e.g. light-weight casts, splints or braces = mobilisation as soon as possible



Treatment

- Metal rods / nails are used to control fractures and improve bowing deformities
- Fractures may still occur post intervention, however nailings provide internal splint and maintain alignment
- 2 types of nail:
 - Expandable*** - telescopic design, change in length during bone growth
 - Non-expandable*** more versatile, may need replacing as child grows
- Due to their thickness – larger bones, femur / tibia
- Anchored both ends using screws

Treatment



Niyibizi (2009)

X-ray of a patient with a severe form of OI.

The skeletal abnormalities of femurs and tibia are evident.

The fractures are usually stabilized by intramedullary rodding as shown in the right femur.



Conclusion

- The diagnosis of OI is based on clinical and radiological features
- Many radiologic findings are nonspecific and may be seen across all subtypes
- The generic differential diagnosis is based upon age at presentation – NAI ? Mechanism of injury
- The gold standard for imaging is plain film
- CT, useful for evaluating neurologic complications and for investigating hearing loss
- MRI, useful for evaluating neurologic complications particularly cord compression
- DEXA sometimes help to establish diagnosis, assess prognosis, monitor treatment response



References

- Allesandro, D. (2008) *PaediatricEducation.Org Case Presentation* <http://www.pediatriceducation.org/2008/04/28/> [viewed 21/06/09]
- Champan, S. (1997) *Non-accidental injury or brittle bones*. *Pediatr Radiol*
- Greenspan, A. (2004) *Orthopedic Imaging – A Practical Approach*. Lippincott Williams & Wilkins. Philadelphia
- Fred, H. (2005) *A valuable physical sign* http://www.residentandstaff.com/issues/articles/2005-07_11.asp [viewed 21/06/09]
- Kirpalani, A. & Babyn, PS. (2008) *Osteogenesis Imperfecta* <http://emedicine.medscape.com/article/411919-print> [viewed 30/04/2009]
- Marlowe, A. (2002) *Testing for osteogenesis imperfect in cases of suspected non-accidental injury*. *J Med Genet*
- Mosby's Dental Dictionary (2008) *Dentinogenesis Imperfecta* <http://medical-dictionary.thefreedictionary.com/dentinogenesis+imperfecta> [viewed 21/06/09]
- NHS Evidence (2005) *Genetic Conditions – Osteogenesis Imperfecta*. <http://www.library.nhs.uk/geneticconditions/viewresource.aspx?resID=112031> [viewed 30/04/2009]



References

- Niyibizi, C. (2009) *Gene therapy approaches for osteogenesis imperfecta* http://www.nature.com/gt/journal/v11/n4/fig_tab/3302199f2.html [viewed 21/06/09]
- Paterson, CR. et al (1993) *Osteogenesis imperfect: the distinction from child abuse and the recognition of a variant form.* Am J Med Genet
- Poznanski, A. (2009) *Paediatric musculoskeletal radiology – The Bone Dysplasias.* http://www.medcyclopaedia.com/library/radiology/chapter14/14_7.aspx [viewed 07/06/09]
- Robben, S. (2006) *Diagnostic Imaging in Child Abuse – Non Accidental Trauma* <http://www.radiologyassistant.nl/en/43c63c41ef792> [viewed 21/06/09]
- Teh, J. (2009) *Osteogenesis Imperfecta* [http://imaging.consult.com/chapter/S1933-0332\(07\)76113-X](http://imaging.consult.com/chapter/S1933-0332(07)76113-X) [viewed 13/05/2009]
- Soo-Hyun, L. et al. (2002) *Fetal Musculoskeletal Malformations with a Poor Outcome: Ultrasonographic, Pathologic, and Radiographic Findings.* http://www.kjronline.org/view_articletext.asp?year=2002&page=113 [viewed 07/06/09]



Questions