Osteogenesis Imperfecta

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Abstract

Osteogenesis imperfecta is caused by mutations in the COL1A1 or COL1A2 genes, resulting in defects in collagen structure or quantity. The clinical spectrum ranges from mild bone fragility to perinatal lethality. Clinical presentation is variable and may include recurrent fractures, osteopenia, hearing loss, vascular fragility, blue-gray sclera, and skeletal deformities. Prenatal diagnosis and monitoring typically involve US and chorionic biopsy with genetic testing, while postnatal evaluation includes radiography, dual-energy x-ray absorptiometry, and confirmatory genetic testing. Management focuses on reducing fracture risk and improving function through bisphosphonates, physical therapy, and surgical stabilization.

Keywords: musculoskeletal, bones, congenital, syndrome

Case Summary

A 5-week-old neonate presented to the emergency department with decreased movement of the right lower extremity.

Imaging Findings

Initial radiograph of the right femur (Figure 1) revealed a transverse, angulated fracture. A subsequent skeletal survey (Figure 2) demonstrated multiple rib fractures, a left clavicle fracture, a fracture through the C2 vertebral body, and numerous Wormian bones within the skull. Head CT (Figure 3) confirmed the C2 vertebral body fracture and multiple Wormian bones and additionally showed absence of the lamina dura surrounding unerupted teeth.

Diagnosis

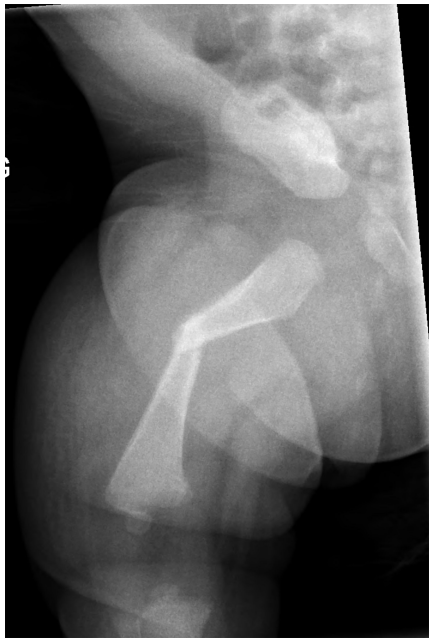
Osteogenic imperfecta.

The differential diagnosis in a child with frequent fractures includes nonaccidental trauma, idiopathic juvenile osteoporosis, hypophosphatemia rickets, osteopetrosis with renal tubular acidosis, as well as various skeletal disorders such as Cole-Carpenter syndrome, Bruck syndrome, severe fibrous dysplasia of bone, and idiopathic autosomal recessive hypophosphatasia. In infants, additional differential diagnoses can include achondrogenesis type 1 and thanatophoric dysplasia.

Discussion

Osteogenesis imperfecta, also known as brittle bone disease, is most commonly an autosomal-dominant disorder, occurring in approximately 1 in 15,000-20,000 live births.[1] The condition encompasses multiple subtypes, with severity ranging from mild bone fragility to perinatal lethality in type 2 disease.[2] An overview of the 4 most common subtypes is included in Table 1.

Figure 1. Radiograph of the right femur showing a transverse fracture of the mid diaphysis.



Most cases are caused by mutations in the COL1A1 and COL1A2 genes, which encode type 1 collagen, leading to either reduced collagen production or structural abnormalities.[2] In osteogenesis imperfecta type 1, frameshift mutations with premature stop codons result in decreased collagen synthesis, a thinner bone matrix, and impaired skeletal mineralization.[2] In contrast,

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Figure 2. (A) Frontal image of the chest, (B) oblique view of the chest, (C) and lateral view of the skull and cervical spine obtained as part of a skeletal survey show multiple healing rib fractures (arrowheads), including multiple fractures within the same rib, a left clavicle fracture (arrow), a fracture through the pedicles of C2 (white arrow), and multiple Wormian bones (dashed arrow).

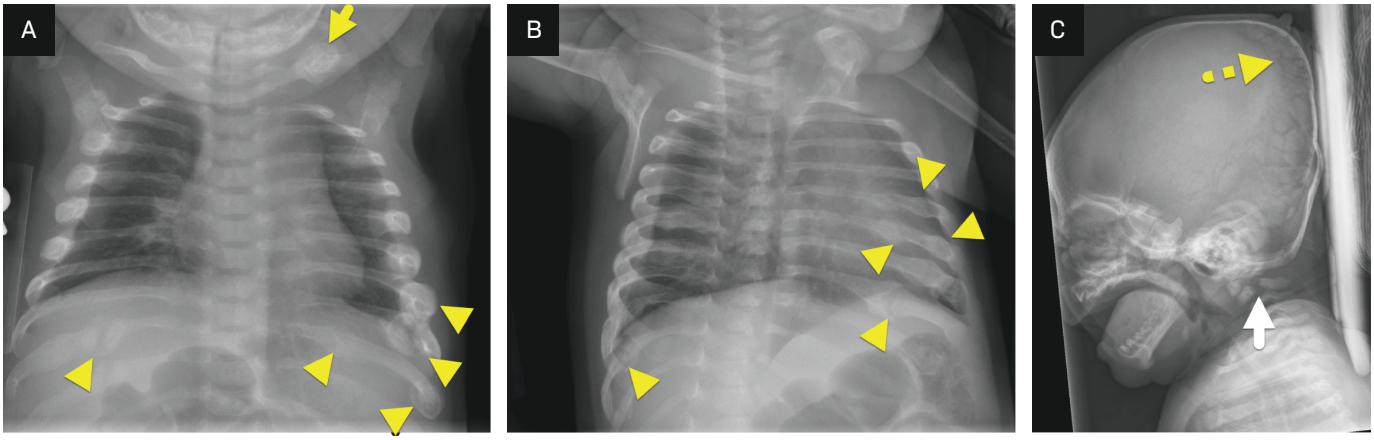
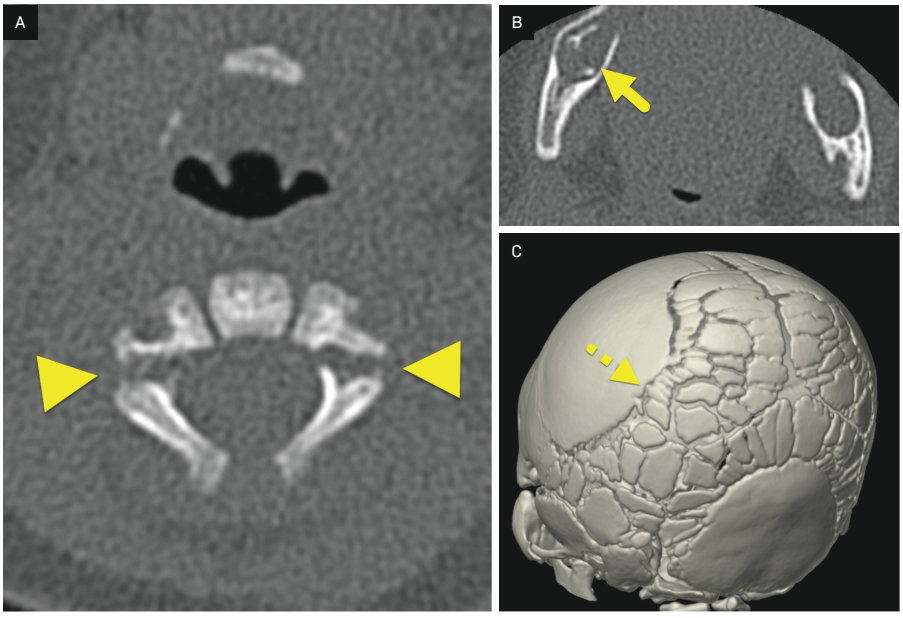


Figure 3. (A) Axial CT image through the C2 vertebral body showing a fracture of both pedicles (arrowheads). (B) Axial CT image through the mandible showing the absence of the normal lamina dura surrounding the teeth (arrow). (C) 3-dimensional reconstruction of the skull showing multiple Wormian bones (dashed arrow).



types 2-4 are typically associated with substitution or deletion mutations that produce structurally defective collagen, causing bone fragility and abnormal bone matrix formation.[2]

Clinically, osteogenesis imperfecta is characterized by recurrent fractures, often beginning in early childhood with the onset of ambulation.[1] Additional skeletal findings include osteopenia, short stature, scoliosis, pectus excavatum, and hearing loss.[3] Beyond the skeleton, the connective tissue disorder affects multiple organ systems, leading to features such as blue or gray sclera, dentinogenesis imperfecta with translucent teeth, joint hyperlaxity, restrictive pulmonary disease, sensory and motor disturbances, vascular fragility, and nephrolithiasis.[2,3]

Diagnosis of osteogenesis imperfecta involves a combination of clinical evaluation, imaging, and genetic testing. In patients with a known family history, prenatal evaluation typically begins with chorionic villus sampling and DNA sequencing.[4] Alternatively, incidental findings on routine prenatal US, such as bone shortening, decreased bone echogenicity, fractures, and rib beading, may raise suspicion for osteogenesis imperfecta and prompt further genetic testing.[5] US can also be used to monitor for complications in fetuses known to have the condition.[4] Transvaginal US is preferred for its ability to detect skeletal abnormalities as early as 14 weeks of gestation, with 3-dimensional imaging offering superior diagnostic detail when combined with 2-dimensional images.[4,6] Fetal MRI can provide additional information, particularly for evaluating extra-skeletal complications such as restricted lung volume in osteogenesis imperfecta type 2.[4]

When diagnostic evaluation begins postnatally, radiography is typically the initial imaging modality of choice. Skeletal surveys are particularly useful for monitoring patients with osteogenesis imperfecta, especially during periods of rapid growth. Radiographic findings may include fractures and diaphyseal bone deformities, flattening of the skull base, basilar invagination, multiple Wormian bones, rib beading, and generalized osteopenia.[4-6] In osteogenesis imperfecta type 3, characteristic features

Table 1. Overview of the 4 Most Common Subtypes of Osteogenesis Imperfecta, Including Inheritance Pattern, Pathophysiology, Unique Clinical Features, and Typical Severity of Presentation

Subtype	Inheritance	Pathophysiology	Unique Clinical Features	Severity
Type 1	Autosomal dominant	Reduced amount of collagen with normal structure	Minimal deformities, blue sclera, conductive hearing loss, mildly impaired growth, dentinogenesis imperfecta in subtypes 1B/1C	Mild
Type 2	Autosomal dominant OR recessive	Severe disruption of collagen function	Extreme bone fragility, beaded ribs, crumpled femora on radiograph	Severe to lethal
Type 3	Autosomal dominant OR recessive	Reduced amount and/or structural dysfunction of collagen	Blue sclera in infancy, severe bone fragility with progressive deformities, basilar invagination, brittle teeth	Mild to severe
Type 4	Autosomal dominant OR recessive	Reduced amount and/or structural dysfunction of collagen	Normal sclera, moderate to severe bone deformity, impaired growth, dentinogenesis imperfecta in subtype 4B	Moderate to severe

There are at least 17 additional subtypes that have been identified.[1-5]

include a "bamboo cane" appearance of abnormally remodeled long bones and "popcorn" calcifications around the knees.[4] Definitive genetic diagnosis of osteogenesis imperfecta is confirmed via skin biopsy.[4]

Because radiography lacks sensitivity for assessing bone density, dual-energy x-ray absorptiometry (DXA) is often used to supplement evaluation and monitoring of osteopenia in patients with osteogenesis imperfecta.[5] CT and MRI are not routinely used but may be helpful for better visualization of cranial structures or soft tissues in select cases.[4,5]

As there is no known cure for osteogenesis imperfecta, management relies on a multidisciplinary approach aimed at reducing fractures and maximizing mobility. Bisphosphonates, such as cyclic intravenous pamidronate and oral risedronate, are commonly used to increase bone density and reduce fracture risk.[1] Surgical stabilization with intramedullary rods and physical therapy are also frequently employed.[1] Emerging treatments under investigation include mesenchymal stem cell therapy, setrusumab (a sclerostin-neutralizing antibody), and bone marrow transplantation.[1,7,8]

Conclusion

Osteogenesis imperfecta is caused by mutations in the COL1A1 or COL1A2 genes, resulting in defects in collagen structure or quantity. The clinical spectrum ranges from mild bone fragility to perinatal lethality. Clinical presentation is variable and may include recurrent fractures, osteopenia, hearing loss, vascular fragility, blue-gray sclera, and skeletal deformities. Prenatal diagnosis and monitoring typically involve US and chorionic biopsy with genetic testing, while postnatal evaluation includes radiography, DXA, and confirmatory genetic testing. Management focuses on reducing fracture risk and improving function through bisphosphonates, physical therapy, and surgical stabilization.

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