Radiographic features of osteogenesis imperfecta

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Abstract
Background Osteogenesis imperfecta (OI), commonly called “brittle bone disease”, is a genetic disorder characterised by increased bone fragility and decreased bone density due to quantitative and/or qualitative abnormalities of type I collagen. Different types of OI exist, from mild to severe; they may lead to death, multiple bone fractures, skeletal deformity and short stature.

Methods Severe cases are usually diagnosed before birth and may incite the parents to choose therapeutic abortion, whereas milder cases are much more difficult to diagnose and may be sometimes confused with non-accidental injury (NAI) (“child abuse”) in young children. Whatever the degree of severity, conventional radiography still remains the mainstay in diagnosing OI.

Results The prognosis of this disorder has changed in the last few years thanks to biphosphonate therapy.

Conclusion The aim of this pictorial review is to illustrate the radiographic manifestations of OI, including in children receiving biphosphonates, and to outline specific patterns that help differentiate OI from NAI when necessary.

Key Points
- The main radiographic features of OI are osteopenia, bone fractures and bone deformities.
- Some radiographic features depend on the type of OI or may be encountered with biphosphonates.

Keywords Osteogenesis imperfecta · Radiography · Biphosphonates · Child abuse

Abbreviations
OI Osteogenesis imperfecta
NAI Non accidental injury
CT Computed tomography
MRI Magnetic resonance imaging

Introduction
Also known as “brittle bone disease”, osteogenesis imperfecta (OI) is a genetic disorder characterised by increased bone fragility and low bone mass density due to quantitative and/or
qualitative abnormalities of type I collagen [1, 2]. It is usually characterised by an autosomal dominant mode of inheritance (95 % of cases), but some cases are related to autosomal recessive traits or to a spontaneous mutation [3].

OI is rare but far from exceptional, affecting approximately 1 in 10,000–20,000 births. In the vast majority of cases, it results from mutations in either the COL1A1 or the COL1A2 gene, encoding the pro-alpha 1 and pro-alpha 2 chains, respectively. These polypeptide chains form a triple helix of intracellular type I procollagen, which is the precursor of extracellular type I collagen. The latter is a component of many tissues such as bone, dental enamel, eye sclera, skin, tendons and ligaments. Genetic mutations affect the spatial arrangement of the polypeptide chains and consequently alter the biomechanical properties of type I collagen, particularly its resistance to stretching. The

| Table 1 | Sillence and Glorieux classification of OI |
|---------|-------------------------------------------|
| Type I OI (mild) | Fractures; minor deformities  |
| | Almost normal stature  |
| | Blue sclerae  |
| | “Dentinogenesis imperfecta” may be present |
| Type II OI (lethal) | Fractures in utero |
| Type III OI (severe) | Fractures; kyphoscoliosis; major deformities  |
| | Very small stature  |
| | Triangular face; variable colour of sclerae  |
| | “Dentinogenesis imperfecta” is frequent |
| Type IV OI (moderate) | Fractures  |
| | Small stature  |
| | Variable colour of sclerae  |
| | “Dentinogenesis imperfecta” may be present |
| Types V, VII and VII have been added to the original classification system (no type I collagen mutation, but abnormal bone on microscopy and similar phenotype) |
| Type V OI | Fractures; hyperplastic callus; interosseous membrane ossification; metaphyseal dense lines  |
| | Normal colour of sclerae  |
| | No “dentinogenesis imperfecta” |
| Type VI OI | Looser striations mimicking fractures |
| | No wormian bones  |
| Type VII OI | Fractures; coxa vara  |
| | Normal colour of sclerae  |
| | No “dentinogenesis imperfecta”  |
| | Rhizomelia |

Fig. 1 Sagittal and transverse US scans in a 26-week foetus with femur length measurements below the 3rd percentile show a shortened and angulated femur with a hypoechoic cleft (arrowhead) suggestive of a fracture (left) and decreased echogenicity of the cranial vault (right). Courtesy of Pr Freddy AVNI, Lille (France)
hallmarks of OI are therefore bone fragility and other connective-tissue manifestations, with a large variation in phenotype.

The classification most widely used for OI distinguishes four types, based on clinical findings and disease severity (Table 1) [3]. More recently, three types whose phenotype is similar to other types of OI but that are not associated with type I collagen mutations have been added by Glorieux et al. [4] (Table 1). This classification is not always easy to use, as some patients cannot be included (and some genetic mutations are still to be discovered), and it is usually more convenient in practice to distinguish between cases diagnosed before or at birth (i.e., severe forms of OI) and cases diagnosed after birth (i.e., milder forms of OI).

**Antenatal diagnosis of OI**

Severe forms of OI (mainly type II) can be diagnosed by ultrasound during the second trimester of pregnancy [5, 6]. Nonspecific signs such as intra-uterine growth retardation or hydramnios may be seen. Otherwise, examination may show abnormalities of the skull, the rib cage, the spine or the limbs, such as decreased echogenicity due to insufficient mineralisation, deformities related to fractures, callus formation and increased bone plasticity, and micromelia, especially of the femur (Fig. 1) [5, 6]. In case of doubt and when a termination of pregnancy is being considered, low-dose computed tomography (CT) with three-dimensional reconstructions of the whole foetal skeleton can be performed, after 26 weeks of gestation, to yield a correct diagnosis. The role of MRI is limited, except when visualisation of the foetal brain or visceral organs is required to look for associated abnormalities or to assess foetal lung volume [7]. When termination of pregnancy is performed based on the discovery of ultrasound and CT abnormalities, postmortem radiographs are a very useful adjunct to diagnosis, in confirming and specifying foetal bone abnormalities (Fig. 2).

**Postnatal diagnosis of OI**

OI encompasses a broad range of presentations, from virtually non-apparent forms to more severe ones, and some may
go unnoticed for a long time. Positive diagnosis can be made clinically on the basis of skeletal and/or extraskeletal manifestations, but this is only the case in severe forms of OI. A family history of OI can also be helpful in arriving at a diagnosis. In fact, in most cases, imaging is required for diagnosis.

Extraskeletal manifestations These are inconstant, but their recognition allows a quicker diagnosis of OI. Extraskeletal manifestations are diverse, related as they are to the ubiquitous presence of type I collagen in the human body: blue sclerae (mainly in type I OI); a greyish or yellowish aspect of the teeth, also called “dentinogenesis imperfecta” (mainly in type III OI); skin fragility; joint and ligament hyperlaxity; early hypoacusia; and cardiovascular abnormalities (particularly aortic valve disease) [3, 4, 8]. Less frequently, neurological abnormalities related to basilar impression and platybasia (mainly in type IV OI) or to direct involvement of neurovascular structures may be encountered [9, 10].

Skeletal manifestations OI is generally recognised in children presenting with multiple, repeated or unexplained fractures, especially when the causative trauma is minor or when there is no history of trauma. Other skeletal manifestations depend on the severity of the disease and may include short stature and progressive deformities.

Fig. 4 Anteroposterior radiographs of the pelvis and foot in a child with OI show severe and diffuse osteopenia with prominent thinning of the metatarsal bones.

Fig. 5 Lateral radiographs of the spine in two children with OI show homogeneous rarefaction (left) and predominant trabecular rarefaction (right) of the cortical and trabecular bone, with a “frame-like” pattern of the vertebrae (right). Note the partial collapse of the L2 and L5 vertebral bodies.

Fig. 6 Anteroposterior radiograph of the humerus in a child with OI reveals a complete fracture of the mid-diaphysis with a detached, triangular fragment.
of the spine (kyphosis, scoliosis), the rib cage or the lower limbs (discrepancy in length, bowing).

**Radiographic findings in OI**

The main radiographic features are osteopenia, bone fractures and bone deformities. They result from constitutional bone fragility (cortical bone thinning, trabecular bone rarefaction) but also from acquired bone fragility due to muscle wasting and immobilisation. None of them are specific enough, but their association, together with a suggestive clinical history (propensity for fractures, family history of presenile loss of hearing, etc.) may suffice to confirm the diagnosis of OI.

**Osteopenia** Radiographs reveal cortical bone thinning and excessive trabecular bone transparency (Figs. 3, 4, 5). This finding, however, is subjective and may be difficult to assess with conventional radiography, and its detection requires a significant reduction (about 30 to 50 %) in calcified bone mass. Bone densitometry by dual-energy X-ray absorptiometry (DEXA) is currently the optimal method to detect decreased bone mineral density, but in children, accurate interpretation of the results requires a good knowledge of the potential pitfalls related to age, sex, pubertal stage and skeletal maturation [11]. Decreased bone mineral density is not specific for OI; it may be encountered in metabolic disorders (hypogonadism, growth hormone deficiency, hyperthyroidism, juvenile diabetes mellitus, calcium and vitamin D deficiency, etc.). However, when such causes have been excluded, DEXA...
may help to establish the diagnosis of OI [12] and to monitor the response to biphosphonates.

**Bone fractures** They affect both the axial and appendicular skeletons. These fractures are similar to those seen in normal children who suffer trauma and usually consolidate within the normally expected times. Some children may have few or no fractures, whereas others experience numerous fractures throughout their lives, especially when they start walking. The most common fractures occur in the long bone diaphyses, the spine and the apophyses. Diaphyseal fractures may be complete (Fig. 6) or incomplete (Fig. 7), and more or less displaced. In the spine, multiple thoracolumbar compression fractures may be seen (Fig. 8). Spondylolysis of L5, with or without consecutive spondyloolisthesis, is also common in children with OI due to a fracture (Fig. 9) or an elongation of the pars interarticularis of L5, all of which are fostered by bone fragility and/or hyperlordosis [13, 14]. Apophyseal avulsion fractures are less common; they are often displaced and sometimes bilateral [15, 16]. They classically involve the olecranon or the tibial tubercle, and usually require internal fixation [15, 16].

**Bone deformities** They most frequently affect the appendicular skeleton, especially the lower limbs, but the upper limbs (Fig. 10) and skull may be involved. These deformities are due to excessive bone malleability and plas- ticity. In the skull, radiography may show a prominent occipital region (so-called the “Darth Vader” appearance) (Figs. 11, 12) or a flattening of the cranial vault with transverse infolding of the cranial base (the so-called “Tam O’Shanter skull”) (Fig. 11); however, such deformities are rare. Much more frequently, radiographs reveal multiple wormian bones (defined as the presence of 10 or more wormian bones [17]) that lend a “mosaic” or “paving” appearance to the cranial vault (Fig. 13). A significant number of wormian bones occur more frequently in more severely affected OI patients [17]. In the long bones, bending (Fig. 14) and thinning of the diaphyses may be seen, sometimes complicated by progressive fractures in the concave aspect of the deformity.
that can recur after healing. Severe residual angulation of a healed fracture constitutes another mechanism accounting for long bone deformities. In the lower limbs, diaphyseal bending or angulation may be responsible for lower leg-length discrepancy. In the pelvis, coxa vara and acetabular protrusion have occasionally been reported.

In toddlers with severe forms of OI (mainly type III), the long bones may appear thick and broad, instead of thin and markedly shortened and bowed (Fig. 15). They exhibit a lack of bone modelling with a “bamboo cane appearance” linked to multiple healed fractures and severe bone deformities of the femur (anterolateral bowing or “shepherd’s crook” deformity) (Fig. 15) and the tibia (anterior bowing or “saber shin” deformity) (Fig. 16).

**Radiographic features depending on the type of OI**

*Hyperplastic callus formation* This has occasionally been reported in type V OI, especially in males and in the femur [18–20]. Hyperplastic callus formation can occur either after a fracture (Fig. 17) or surgery or spontaneously, and may mimic osteosarcoma clinically and radiographically. In this case, CT and MRI are useful to...
avoid misdiagnosis, as they will respectively detect the absence of osteolysis and of bone marrow infiltration. CT may reveal an occult fracture, whereas MRI may show a thick calcified rim with low signal on T1- and T2-weighted images at the periphery of the callus [18–20]. Hyperplastic callus formation is not specific to OI; it can also be seen in children with spinal dysraphism or with subperiosteal hematomas related to NAI, bleeding disorders or neurofibromatosis.

Ossifications of the interosseous membrane These are encountered in type V OI, in the forearm (Fig. 18) or leg, and may be associated in some cases with a congenital dislocation of the radial head [20, 21].

“Popcorn” calcifications They are more commonly seen in type III OI, in the metaphyseal and epiphyseal regions of the knee (Fig. 19), and may contribute to femoral growth deficiency and lower leg-length discrepancy [22, 23]. These intraosseous calcifications are thought to result from microtraumatic fragmentation and disordered maturation of the growth plate.

Dense metaphyseal bands These are usually encountered in children with OI receiving biphosphonates, but have been reported in type V OI independently of any treatment. Dense metaphyseal bands can also be seen in children receiving biphosphonates for secondary osteoporosis (cerebral palsy, glucocorticoid-treated disorders, etc.).

Radiographic findings with biphosphonate therapy

Biphosphonates are potent inhibitors of osteoclast-mediated bone resorption and have demonstrated clinical usefulness in the treatment of children with severe forms
of OI [24]. The treatment usually consists of cyclic intravenous infusions and may be initiated after birth. Several studies have reported beneficial effects of bisphosphonates on pain, mobility, growth, bone mineral density and bone turnover and fracture rate [25–28]. However, long-term effects of these agents on the immature growing skeleton have to be assessed.

On radiographs, specific findings in children receiving bisphosphonates include increased bone density in the spine and long bones, as compared with previous radiographs, dense metaphyseal lines (so-called “zebra lines”), very similar to Harris growth arrest lines, and dense metaphyseal bands. In long bones, these lines are parallel to the growth plate; they are located in the metaphysis and move towards the diaphysis in step with bone growth (Fig. 14). Each dense line corresponds to one intravenous course, and the space between two lines depends on the bone growth rate and delay between two courses. When multiple, these lines are responsible for a “ladder-rung” appearance (Fig. 14). In the spine or in the flat bones, apophyses and epiphyses, a “bone-within-a-bone” pattern, which may be considered to be the equivalent of metaphyseal dense lines in long bones, may be observed (Fig. 20) [29]. When there is less bone growth between courses of the drug, the metaphyseal lines are more closely spaced and appear as dense metaphyseal bands (Figs. 14, 16) and dense vertebral endplates.

**Differential diagnosis of OI**

A positive diagnosis of OI can be difficult, particularly in young children (before the age of 2 years) with mild forms of OI (types I, IV) and when there are few or no obvious extraskeletal manifestations and no familial history of increased bone fragility. These cases of OI may be tragically mistaken for NAI. Indeed, in both OI and NAI, unexplained, multiple and repeated fractures may occur; children may present with bruises and contusions; radiographs may reveal different types of fractures, fractures of various ages that went undetected and no evidence of osteopenia. A thorough radiographic examination, including a skeletal survey, can help differentiate between OI and NAI (Table 2). In NAI, some fractures are very suggestive of abuse (i.e., posterior rib fractures, metaphyseal corner fractures and complex skull fractures) [30, 31].

**Fig. 19** Anteroposterior radiograph of the knee in a child with type III OI and a history of femoral osteosynthesis evidences “popcorn” calcifications (arrows) with sclerotic margins.

**Fig. 20** Lateral radiograph of the spine and oblique lateral radiograph of the foot in a child with OI receiving bisphosphonate therapy reveal a “bone-within-a-bone” pattern of the vertebral bodies and the cuboid bone (arrowheads). Note also the presence of sclerotic lines inside the base of the fifth metatarsal bone (arrow).
**Posterior rib fractures** Rib fractures usually result from anteroposterior compression of the rib cage when the child is held around the chest and violently shaken back and forth. The posterior involvement is due to excessive leverage of the posteromedial part of the rib over the transverse process of the spine and is highly specific of abuse [30, 31]. In this situation, posterior rib fractures are frequently multiple on radiographs and are often associated with callus formation when discovered (Fig. 21).

**Metaphyseal corner fractures** Long bone fractures may be encountered in NAI, but in contrast to OI, where the fractures most commonly affect the diaphyseal regions, they classically involve the metaphysis, especially that of the distal femur (Fig. 22), the proximal and distal tibia and, less frequently, the proximal humerus [30, 31]. Metaphyseal corner fractures, also known as classic metaphyseal lesions, are virtually pathognomonic for abuse [32]. They are due to shearing forces applied to the child’s extremities when shaken. The fracture lines

| Radiographic signs          | Typical OI | Typical NAI | Overlapping |
|----------------------------|------------|-------------|-------------|
| Osteopenia                 | Yes        | No          |             |
| Multiple fractures         | Yes        | Yes         |             |
| Fractures of various ages  | Yes        | Yes         |             |
| Diaphyseal fractures       | Yes        | Yes         |             |
| Classic metaphyseal lesions| No         | Yes         |             |
| Long bone deformities      | Yes        | No          |             |
| Skull deformities          | Yes        | No          |             |
| Multiple wormian bones     | Yes        | No          |             |
| Complex skull fracture     | No         | Yes         |             |
| Vertebral fractures        | Yes        | Yes         |             |
| Spinous process fractures  | No         | Yes         |             |
| Posterior rib fractures    | No         | Yes         |             |
| Anterior / lateral rib fractures | Yes   | Yes         |             |
| Hyperplastic callus formation | Yes   | Yes         |             |
| Apophyseal avulsion fractures | Yes  | No          |             |
| Interosseous ossifications | Yes (type V) | No      |             |
| “Popcorn” calcifications   | Yes (type III) | No     |             |
| Dense metaphyseal bands    | Yes (V, BP) | No          |             |

*BP* biphosphonates
are grossly horizontal, parallel to the growth plate, and detach a “frisbee-shaped” bone fragment (i.e., a fragment that is thin centrally and thick peripherally) [31]. On radiographs, metaphyseal fractures appear as “corner” (Fig. 22) or “bucket-handle” (Fig. 23) fractures, depending on the size of the avulsed piece of bone (Fig. 24) and its relation to the X-ray beam. These fractures may be bilateral and symmetric on radiographs, which is another interesting finding in favour of the diagnosis of NAI (Fig. 22).

**Complex skull fractures** Skull fractures are relatively common in both non-accidental and accidental injuries, and result from direct trauma. Bilateral fractures, fractures involving more than one cranial bone, fractures evidencing a complex configuration (Fig. 25), fractures that cross suture lines, depressed, wide (diastasis ≥ 3 mm) and growing fractures and fractures associated with underlying intracranial lesions all suggest NAI [31].

Other fractures such as sternal, scapular and spinous process fractures are also highly specific for NAI, but they are rarely encountered in practice.

Other disorders such as copper deficiency, Menkes disease (a genetic disorder of copper metabolism, also known as kinky hair disease), scurvy and vitamin D deficiency rickets may also cause diagnostic difficulties in children with unexplained fractures and be confused in some cases with NAI [33, 34]. However, medical history, clinical manifestations, biochemical and radiological findings allow a correct diagnosis in most cases. In copper deficiency and Menkes disease, fractures are usually noted within the first 6 months of life; they are associated with hypopigmented, and brittle hair and progressive neurologic deterioration in Menkes disease. Typical radiographic findings include osteopenia, bone age retardation, increased density of the provisional zone of calcification and symmetrically distributed metaphyseal abnormalities (cupping and fraying, “sickle-shaped” spurs and fractures) [34]. In scurvy, there is no cupping or fraying of the metaphyses, but radiography shows evidence of radiolucent metaphyseal bands beneath the increased density of the provisional zone of calcification and/or periosteal reaction [34]. In rickets, metaphyseal abnormalities similar to copper deficiency
are seen on radiographs but with decreased density of the provisional zone of calcification and increased width of the growth plate [34].

**Conclusion**

OI should be suspected in all children presenting with increased bone fragility, including fractures that occur with little or no trauma. Positive diagnosis is typically made on the basis of personal and familial medical history, physical examination (preferably with a clinician who is familiar with OI), radiography and, in some cases, complementary investigations such as bone densitometry, biochemical tests or DNA-based sequencing. On radiographs, OI has no pathognomonic features, but some of them may be suggestive of the diagnosis. Recent advances in the treatment of OI with biphosphonates have resulted in radiographic findings, of which the physician must be aware. Usually differentiating OI from NAI is not difficult in young children, though the issue is often raised in court in the defence of cases of NAI, but if necessary radiography is very useful for the differential diagnosis.

**Fig. 24** Diagram of a classic metaphysseal lesion depicts a “corner” incomplete fracture (left) and a “bucket-handle” complete fracture (right). M = metaphysis; E = osseous portion of the epiphysis; ca = cartilaginous portion of the epiphysis. The black line corresponds to the fracture line

**Fig. 25** Anteroposterior and lateral radiographs of the skull in a child having undergone NAI exhibit a complex fracture. The fracture lines (arrows) are bilateral and cross the sutures.
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