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OSTEOGENESIS IMPERFECTA: 
A CURRENT OVERVIEW OF MUSCULOSKELETAL 
RADIOLOGY AND NEW GENETIC CONCEPTS

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SUMMARY – Osteogenesis imperfecta is a genetically and clinically heterogeneous disorder of bone and connective tissue characterized by osteoporosis, fragile bones, hyperextensible joints, dentinogenesis imperfecta, bluish coloration of the sclerae, and adult-onset hearing loss. Medical history, careful physical examination, radiographic features of fractures, and biochemical analysis of skin collagen are the four cornerstones of accurate diagnosis. As osteogenesis imperfecta affects the whole skeleton, radiologic diagnostic features could be seen on any bone at any age of the patient. A radiology specialist should be aware of subtle changes seen on radiographs of axial skeleton (i.e. skull, spine and pelvic bones) and appendicular skeleton (i.e. long and short bones of extremities) as well as of specific osteogenesis features (i.e. "popcorn" calcifications) and difficult differential diagnosis (i.e. hypertrophic callus formation versus osteosarcoma; child abuse fractures versus true osteogenesis imperfecta). About 300 different mutations have been identified within COL1A1 and COL1A2 genes that encode the chains of type I collagen. More than 90% of these are heterozygous single base pair mutations unique to the affected individuals within families. Depending on the location of the mutation within the collagen gene, these produce a variety of clinical pictures which range from mild (OI type 1), lethal (OI type 2) to severely deforming (OI type 3) and mildly deforming (OI type 4). Each of the four types has a common radiologic appearance that helps in establishing the diagnosis. However, recent findings have confirmed that new genes other than type I collagen could be responsible for three new types of OI (OI type 5; OI type 6 and rhizomelic OI). Here we describe the complexity of the phenotype-genotype correlation in OI, and the recently proposed new classification.

Introduction

Osteogenesis imperfecta (OI) or brittle bone disease represents a wide spectrum of genetically and clinically heterogeneous disorder of bone and connective tissue.

Clinical expression of OI varies with age of the patient and is characterized by osteoporosis, bone fragility, hyperextensible joints, dentinogenesis imperfecta, blue sclerae and adult-onset hearing loss. OI is one of the most common skeletal dysplasias, with the incidence of one patient per 25,000 to 40,000 live births1.

For a radiology specialist, OI may have peculiar features as its radiologic signs can be seen on the whole skeleton, and occasionally these signs may have unusual appearance and have hidden significance2. The purpose of this article is to give an as comprehensive as possible re-
view of the radiological picture of OI in pediatric and adult patients. Special emphasis will be given to specific radiological prognostic features as well as to the differential diagnosis.

Axial skeleton

In the natural history of OI, a few subtle anatomical changes can occur on axial skeleton, e.g., skull, spine, pelvis. Radiology specialists should look for them and be very cautious not to oversee those changes that could have a significant impact on the health status of the individual with OI.

Skull

Basilar impression (BI) is a progressive and serious complication in OI patients, with an overall frequency of 25%5. Patients with OI type III and type IVB have an even higher frequency of BI of up to 71%.6 BI denotes elevation of the floor of the posterior cranial fossa as well as medial migration of occipital condyles and infolding of the foramen magnum margins.6 The catastrophic sequel of BI include brain stem compression, tetraplegia, respiratory arrest and sudden death.7 The diagnosis of BI is a radiographic one.6 In radiological evaluation of BI, the initial step is plain lateral cervical spine and cranial radiograph. Translation of the upper cervical vertebral column into the posterior fossa could be noticed on the radiogram. Lateral cranioimetry by drawing lines is a conventional way to measure the degree of BI. There are three lines that are used, i.e. McRea’s, Chamberlain’s, and McGregor’s, McGregor’s line, which is the most useful one, is drawn from the upper surface of the posterior edge of the hard palate to the lowest point of the occipital curve of the skull. The measurement is considered pathological when the tip of the dens projects by more than 7 millimeters above McGregor’s line.6, 6

In the infant age group, there is an important radiological feature seen on anteroposterior and lateral skull radiographs, which is of value in confirmation of the clinical diagnosis of OI. Wormian bones named after the Danish anatomist Olaus Wormius, who described them as small, irregular bones, are found in the cranial sutures.9 These bones are found in all patients with OI in a significant proportion, i.e. their number was greater than 10, they measured more than 6 x 4 millimeters, and were arranged in a mosaic pattern.9 Although wormian bones have a diagnostic significance for OI, they could also be seen in other skeletal dysplasias.9, 10

Spine

Severe scoliotic deformity of the thoracic and lumbar spine is a difficult problem to be effectively treated, and the patient’s respiratory function is usually seriously compromised (Fig. 1 a,b). In children with OI, the incidence and severity of scoliosis is increasing with the type and severity of disease as well as with age.12 The prevalence of scoliosis in the OI population was found to be as high as 75% in 102 patients; 56 patients had scoliosis of less than 40 degrees and 20 patients had scoliosis of more than 40 degrees.13 On lateral radiographs of the spine, four types of the vertebral body shape were identified as a predictor of progressive scoliotic spinal deformity.14 The vertebral body shape could be considered biconvex, flattened, wedged, or unclassifiable. In the presence of six or more biconvex vertebral before puberty, severe scoliosis, i.e. more than 50 degrees, is very likely to develop.14 As a general rule, the natural history of scoliosis in patients with OI is curve progression. Hanscom et al. used radiographic criteria to identify six grades (A-F) of the disease that would indicate scoliosis progression.15 They have concluded that patients with type A disease have a mild form of OI and could benefit from arthrodesis of the spine if indicated by the disease severity and progression. Patients with grade F disease have a severe form of OI that is incompatible with survival. Patients with B, C, D and E type disease have progressive scoliosis but with variable results of spine arthrodesis.15

Patients with OI type III could show particular deformities of axial skeleton, which were not seen in other types of the disease. Vertebrae with marked elongation of the pedicles and posterior rib angulation were not seen in other types of the disease.16 Spondylolisthesis of fifth lumbar vertebra in an adult patient could result from OI due to osteofragility in pars interarticularis and subsequent fracture.17 Vertebral fracture of the lumbar spine following minor trauma in apparently healthy individuals could be the first sign of type I OI. In atypical osteoporosis and circumstances of relatively minor trauma, the diagnosis of OI type I should be considered with help of detailed family history and invasive diagnostic procedures, i.e. skin fibroblast analysis and bone biopsy.18, 19

Pelvis

The prevalence of acetabulum protrusion in patients with OI is approximately 30% in patients with type III and type IV of disease in particular.20 Severe bilateral protrusion of the acetabulum can cause distal obstruction
of the colon due to the narrowed pelvis impinging on the sacrum\textsuperscript{21}. Chronic constipation and abdominal pain were more common in patients with OI who had protrusion of the acetabulum. In these patients, gastrointestinal specialist consultation is advised to prevent the potential problems\textsuperscript{22}. The supra-acetabular region of the ilium could have been the site of expansible lytic bone cyst in a six-year-old boy with OI. This could be a potential diagnostic problem because one should consider osteomyelitis or more aggressive bone changes\textsuperscript{23}.

**Appendicular skeleton**

In patients with OI, due to more mechanical stress, the occurrence of fractures, pseudarthrosis, deformities and osteoarthritis are more common in lower extremities. Consequently, medical literature on the issue of upper extremity problems in patients with OI is quite scanty\textsuperscript{24,25}.

**Upper extremity**

Upper limb problems, e.g., humerus and forearm fractures and deformities, are more often seen in patients with severe forms of OI. However, there is a specific fracture of the forearm that is highly suspected of OI. Bilateral isolated olecranon fracture after trivial or minor trauma indicates that the diagnosis of OI is very likely\textsuperscript{26,27} (Fig. 2 a,b,c,d). Radial head dislocation is another unusual problem on the upper limb, which may show the possibility of the new type of OI (type V). Aneurysmal bone cyst of the radius in a patient with OI three years after fracture has been described\textsuperscript{28}. When the hand function is severely compromised due to forearm deformity, surgical treatment should be considered.
Fig. 2 (a,b,c,d): Bilateral isolated olecranon fracture after minor trauma in a 10-year-old boy is suggestive of the osteogenesis imperfecta diagnosis (a,b). Postoperative X-ray after fracture fixation with K-wires (c,d).

Lower extremity

Fractures of long bones on lower extremity can occur in two patterns. In the first group are those patients who sustained fractures after fall or similar injury. Fracture is easily diagnosed and managed by standard procedures. Second group of patients feel pain or discomfort after sudden muscle contraction. Patients suffer from pain that is not of long duration and dislocation of the fragments is small or there is no dislocation. This makes the diagnosis of avulsion fracture difficult. For the diagnosis of avulsion fracture, one needs a high rate of suspicion and diagnosis confirmation is made with radiographs (Fig. 3).
Fig. 3. Lateral X-ray view of fracture with no dislocation at the lowest point of the osteosynthesis plate, due to sudden muscular contraction in a patient with type 1 osteogenesis imperfecta.

This type of fracture can in general be treated with lightweight cast immobilization and early mobilization to minimize disuse osteoporosis. When avulsion fracture is late or misdiagnosed, slowly progressive bowing is likely to occur (Fig. 4 a,b). Current management of typical long bone fracture and bowed long bone deformity in children is the application of an elongating intramedullary nail with simultaneous correction of pre-existing deformity. A modern radiology technique facilitates to perform surgery with minimal trauma, good rod diameter prediction, and easy exchange of telescoping rod system when the rod is about to disengage.

If long bone is not protected by intramedullary rodding, limb shortening, deformity and non-union may develop following fracture in some patients with OI (Fig. 5 a,b,c,d). In adult patients with OI who can walk, osteoarthrosis of the hip and knee may be an additional orthopedic problem. These patients can be treated with total joint replacement with special care to avoid acetabular protrusion on hip joint replacement. Further, in some rare circumstances, in adults with OI reflex sympathetic dystrophy syndrome and transient osteoporosis may develop. Magnetic resonance imaging (MRI), computed tomography (CT), bone scan, and bone biopsy can be helpful on assessing these conditions.

Bone mineral density (BMD) is generally decreased in patients with OI. Assessment of BMD from plain radiographs is not very accurate. Dual-energy X-ray absorptiometry (DEXA) is a reproducible and objective method of BMD measurement in children, who may have approximately 75% BMD of normal. In post-menopausal women, decreased BMD reflects superimposition of the age related bone loss with OI related osteopenia.

**Epiphysis and metaphysis**

In a growing child with OI, peculiar changes may be observed in the region of metaphysis and epiphysis. So-called "popcorn" calcifications appear on radiographs as clusters of low radiolucencies with sclerotic margins. They were found in 87% of cases in the lower extremity, predominantly around the knees and ankles (Fig. 6). These "popcorn" calcifications can result from fragmentation and disordered maturation of the physis. Their presence may be a sign of disturbances in enchondral ossification with contribution to the severe growth retardation observed in OI.

**Prognosis and differential diagnosis**

It is well known that OI has a great spectrum of variety of skeletal changes that can be seen in neonates and
during the first ten years of life\textsuperscript{42,43}. Spranger and co-workers have devised a scoring system of radiographic features to help predicting favorable prognosis\textsuperscript{42}. They have concluded that a subgroup of patients with marked bowing of lower extremities, mild involvement of the rest of the skeleton, and white sclerae have a particularly fa-
vorable prognosis. A longitudinal study in 127 children with OI during the first ten years of life showed that skeletal changes at birth were significantly more severe in type III than in type IV patients. In young children, one should consider hypophosphatasia, rickets, idiopathic juvenile osteoporosis, and rarely leukemia as a differential diagnosis. Two points are especially important in the differential diagnosis of OI: in pediatric age group, non-accidental injury versus OI; and in adults, osteosarcoma versus hyperplastic callus formation in OI.

Although OI is much less common than child abuse (non-accidental injury), one should keep in mind that children with OI are not immune to non-accidental injury. There are some skeletal fractures in children younger than three years of age that are highly associated with non-accidental injury. These are multiple fractures at different stages of healing, posterior rib fractures, metaphyseal corner fracture, fractures of scapulae, vertebrae and clavicles, spiral fractures of femur and humerus, and bilateral fractures. When the diagnosis of OI or non-accidental trauma is unclear, medico-legal implications could be serious (Fig. 7). Therefore, in such circumstances, a number of specialists in various disciplines (radiology, orthopedics, genetics and pediatrics) must coordinate work together to arrive at the proper diagnosis. The existence of a temporary brittle bone disease (TBBD) is suggested by Paterson et al. Joint laxity was frequent in families of patients with TBBD; infants were usually born preterm and in twins; multiple fractures, especially in the ribs, occur without evidence of trauma in the first six months of life. Child abuse can be excluded by confidence in these patients because, when children are returned to their parents, no subsequent evidence of fracture is found. Other authors could demonstrate association of decreased fetal movement and osteopenia in patients with TBBD, but still its existence is more a matter of clinical opinion than high science.

Serious diagnostic difficulties could be encountered when it is necessary to differentiate osteosarcoma, which is rarely associated with OI, and hyperplastic callus formation, which is also an unusual but benign complication of OI (Fig. 8 a,b,c). MRI and CT studies are recommended for better imaging of the multilayered nature of the lesion and identification of the fracture line. However, a debate of pro-biopsy and no-biopsy proponents is still going on. In conclusion, careful synthesis and interpretation of clinical, laboratory and imaging data is essential for correct and timely diagnosis.

Molecular basis of osteogenesis imperfecta

More than 300 different mutations have been identified within COL1A1 and COL1A2 genes. It is estimated that these mutations are present in at least 90% of all patients with OI. However, most of these mutations are single base pair mutations unique to all affected individuals within families.

Generally speaking, there are two main types of mutations involving the COL1A1 and COL1A2 genes in patients with OI: dominant negative mutations and null allelic mutations. Dominant negative mutations produce abnormalities in the sequence of different regions of the type I collagen gene, and result in expression of a mutant protein that severely affects the normal triple-helix formation (responsible for deforming forms of OI: types II, III, IV, V, VI and rhizomelic OI). The most common dominant negative mutations are glycine substitution mutations in the helical domain of the collagen chain. Further, a different mutation at the donor or acceptor site of collagen gene can cause exon skipping, which eventually results in shortened collagen mRNA and shortened pro alpha chains that drastically affect the normal triple helix configuration. An exception to the statement that severe disease results from a dominant negative mutation in either type collagen gene is null mutation of the COL1A2 gene.

On the other hand, null allelic mutations reduce total collagen by approximately 50%, since a half of the COL1A1 mRNA is retained within nuclear compartment (responsible for nondeforming form of OI; type I OI). Several studies in patients with type I OI who had a substitution at the +1 position of donor splice-site, which caused total intron, confirmed retention of the mutated mRNA within nuclear compartment. More precisely, mutant mRNA with retained intron enter a specific region within the nucleus, SC-35 domain, but their exit is impeded. Therefore, it appears that SC-35 domain in certain cases has an important role in screening and entrapping mutant COL1A1 RNA. The final result is a reduced production of type I collagen but complete organization of the collagen molecule is preserved. In some additional cases, the underproduction of collagen chains can be either transcripational (mutations reduce transcripts of the gene), posttranscriptional (intrion retention, frame shift mutations or stop codon mutations produce a nonfunctional RNA), translational (mutations occur within the region of polyadenylation sequence and other sequences important for transcripational termination cleav-
age and polyadenylation) or posttranslational (mutations alter the amino acid composition of the C-terminal propeptide necessary for chain assembly).

Glorieux and his group have recently described novel forms of OI where no alterations in the structure of two genes encoding the type I collagen molecule could be found. Therefore, a new molecular and clinical classification of osteogenesis imperfecta has been recently proposed (Table 1).
### Table 1. Clinical and molecular classification of osteogenesis imperfecta (OI)

<table>
<thead>
<tr>
<th>Molecular classification</th>
<th>Clinical classification</th>
<th>Clinical severity</th>
<th>Molecular mechanism</th>
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<tbody>
<tr>
<td>Dominant</td>
<td>Type II</td>
<td>Perinatal lethal</td>
<td>Glycine substitutions preferentially located in C terminal helical domain of either collagen chain</td>
</tr>
<tr>
<td></td>
<td>Type III</td>
<td>Progressive deforming</td>
<td>Glycine substitutions preferentially located in mid helical domain of either collagen chain</td>
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<tr>
<td></td>
<td>Type IV</td>
<td>Moderately deforming</td>
<td>Glycine substitutions preferentially located in mid helical domain of the a2 collagen chain</td>
</tr>
<tr>
<td></td>
<td>Type V</td>
<td>Moderately Deforming</td>
<td>Non type I collagen gene mutation</td>
</tr>
<tr>
<td></td>
<td>Type VI</td>
<td>Moderate to severe deforming</td>
<td>Non type I collagen gene mutation</td>
</tr>
<tr>
<td>Rhizomelic</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Haploid</td>
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<tr>
<td></td>
<td>Type I</td>
<td>Classical mild OI</td>
<td>Complete non-functional Coll1A1 allele usually due to premature stop codon</td>
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### References


Sažetak

OSTEOGENESIS IMPERFECTA: PREGLED SUVREMENIH SPOZNAJA O RADIOLOGIJI KOŠTANOГ SUSTAVA I NOVE GENETSKE SPOZNAJE


Osteogenesis imperfecta (OI) je genetski i klinički heterogena bolest kosti i vezivnoga tkiva s određnicama: osteoporozu; lomljivost kostiju; labavost zglobova, dentinogenesis imperfecta; plavćaste bijeločnice i nagluho u odrasloj dobi. Ključ točne dijagnoze su četiri bitna postupka: precizna anamnезa; pažljiv fizikalni pregled; uočavanje radioloških značajki prijeloma i promjena kostiju i biokemijska analiza kolagena kože. Ubacivajena je podjela na četiri tipa OI: od blagog (tip 1), lethalnog (tip 2) do te ko deformirajućeg (tip 3) i umjereno deformirajućeg oblika (tip 4). Svaki od četiri tipa ima zasebne radiološke značajke koje pomažu kod postavljanja točne dijagnoze i klasificiranja. Dijagnostičko-radiološki znaci postoje na cijelom mišićno-konnatalnom sustavu od novo rođenog do kasne životne dobi. Za radiologa je važno prepoznati brojne simptome i specifične promjene na rendgenogramima aksijalnog (lubanja, kralje-nica, zdjelica) i apendikularnog (kosti udova) skeleta. Značaj korisni u diferenciranju osteosarkoma prema stvaranju hipertrofičnog konatalnog kalusa kod OI i drugi posebni znaci bolesti, primjerice metafazne "popcorn" kalcifikacije, prepoznaju se dobrom radiološkom obradom. Dosad je otkriveno oko 300 različitih mutacija na COL1A1 i COL1A2 genima odgovornima za oblikovanje lanaca kolagena tip I. Klinička slika OI razlikuje se prema mjestu mutacije u genu za kolagen. Nedavni nalazi su potvrdili da i drugi geni, uz kolagen tip I, mogu biti odgovorni za nastanak tri nova tipa OI: tip 5; tip 6 i rizomelični tip OI. Nadaže, u tekstu je opisana složenost fenotipske i genotipske korelacije, kao i nedavno predložena nova klasifikacija OI.