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.
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%6. Patients with OI type III and type IVB have an even higher frequency of BI of up to 71%3-5. 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 margins6. The catastrophic sequels of BI include brain stem compression, tetraplegia, respiratory arrest and sudden death7. The diagnosis of BI is a radiographic one6. 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 craniometry 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’s6,8. 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 line3,6.

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 sutures9. 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 pattern9. Although wormian bones have a diagnostic significance for OI, they could also be seen in other skeletal dysplasias9,10.

**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 compromised11 (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 age12. 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 degrees13. On lateral radiographs of the spine, four types of the vertebral body shape were identified as a predictor of progressive scoliotic spinal deformity14. The vertebral body shape could be considered biconcave, flattened, wedged, or unclassifiable. In the presence of six or more biconcave vertebral bodies before puberty, severe scoliosis, i.e. more than 50 degrees, is very likely to develop14. 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 progression15. 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 arthrodesis15.

Patients with OI type III could show particular deformities of axial skeleton, which were not seen in other types of the disease. Vertebral bodies with marked elongation of the pedicles and posterior rib angulation were not seen in other types of the disease16.

Spondylolisthesis of fifth lumbar vertebra in an adult patient could result from OI due to osteofragility in pars interarticularis and subsequent fracture17.

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 biopsy18,19.

**Pelvis**

The prevalence of acetabulum protrusion in patients with OI is approximately 30% in patients with type III and type IV of disease in particular20. Severe bilateral protrusion of the acetabulum can cause distal obstruction
Fig. 1 (a,b): Clinical view (a) and anteroposterior X-ray (b) of the spine in a 16-year-old girl with type III osteogenesis imperfecta. Severe scoliotic deformation compromises pulmonary function.

of the colon due to the narrowed pelvis impinging on the sacrum. 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. 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.

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.

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. 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. When the hand function is severely compromised due to forearm deformity, surgical treatment should be considered.
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).
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.29. 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.30-32.

If long bone is not protected by intramedullary rodding, limb shortening, deformity and non-union may develop following fracture in some patients with OI33,34 (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.35. 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.36,37. 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 OI38,39. 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.38. 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.40,41 (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.40

**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
Fig. 5 (a,b,c,d) X-ray anteroposterior (a) and lateral (b) view of proximal femur to show pseudarthrosis after non-treatment of fracture in a 16-year-old girl with type I osteogenesis imperfecta. After surgical correction of malposition and fixation with plate and screws, pseudarthrosis healed (c,d).

Fig. 6 Anteroposterior X-ray of both knees of a 6-year-old girl with type III osteogenesis imperfecta. Typical “popcorn” calcifications in the region of epiphysis and metaphysis.

Fig. 7 Bilateral fractures of humerus in a neonatus could rise suspicion of non-accidental trauma. In this case, other typical findings are missing.

during the first ten years of life. Spranger and co-workers have devised a scoring system of radiographic features to help predicting favorable prognosis. 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-
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 mRNA. 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 transcriptional (mutations reduce transcripts of the gene), posttranscriptional (intron retention, frame shift mutations or stop codon mutations produce a non-functional RNA), translational (mutations occur within the region of polyadenylation sequence and other sequences important for transcriptional 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\textsuperscript{61-63}. Therefore, a new molecular and clinical classification of osteogenesis imperfecta has been recently proposed\textsuperscript{64} (Table 1).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image}
\caption{(a,c) Fracture of the femur conservatively treated (a); development of hyperplastic callus formation gives rise to the question of possible osteosarcoma (b); CT imaging could help establish correct diagnosis (see text). (Courtesy Head Doctor Boštjan Baebler, Ljubljana).}
\end{figure}
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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<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>
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<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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<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>
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<td></td>
<td>Type V</td>
<td>Moderately Deforming</td>
<td>Non type I collagen gene mutation</td>
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<td></td>
<td>Type VI</td>
<td>Moderate to severe deforming</td>
<td>Non type I collagen gene mutation</td>
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<tr>
<td></td>
<td>Rhizomelic OI</td>
<td>Moderate to severe deforming</td>
<td>Non type I collagen gene mutation</td>
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<tr>
<td>Haploid</td>
<td>Type I</td>
<td>Classical mild OI</td>
<td>Complete non-functional Col1A1 allele usually due to premature stop codon</td>
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References

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


OSTEOGENESIS IMPERFECTA je genetski i klinički heterogeni bolest kosti i vezivnoga tkiva s odrednicama: osteoporoza; lomljivost kostiju; labavost zglobova, dentinogenesis imperfecta; plavčaste bjeloočnice i nagluhost u odrasloj dobi. Ključ točne dijagnoze su četiri bitna postupka: precizna anamneza; pažljiv fizikalni pregled; uočavanje radioloških znakova prijeloma i promjena kostiju i biokemijska analiza kolagena kože. Uobičajena je podjela na četiri tipa OI: od blagog (tip 1), letalnog (tip 2) do tečko deformirajućeg (tip 3) i umjereno deformirajućeg oblika (tip 4). Svaki od četiri tipa ima zasebne radiološke znakove koji pomažu kod postavljanja točne dijagnoze i klasificiranja. Dijagnostičko-radiološke znakove postoje na cijelom mišićno-kostanom sustavu od novorođenca do kasne životne dobi. Za radiologa je važno prepoznati brojne slike i specifične promjene na rendgenogramima aksijalnog (lubanje, kraljevica, zdjelica) i apendikularnog (kostna udova) skeleta. Znaci korisni u diferenciranju osteosarkoma prema stvaranju hipertrofičnog koštanog kalusa kod OI i drugi posebni znaci bolesti, primjerice metafizne "popcorn" kalcifikacije, prepoznaju se dobrom radiološkom obradom. Dosad je otkriveno oko 300 različitih mutacija na COL1A1 i COL1A2 genima odgovornim za oblikovanje lanaca kolagena tip I. Klinička slika OI razlikuje se prema mjestu mutacije na genu za kolagen. Nedavni nalazi su potvrdili da i drugi geni, uz kolagen tip 1, mogu biti odgovorni za nastanak tri nova tipa OI: tip 5; tip 6 i rizomelicni tip OI. Nadalje, u tekstu je opisana složenost fenotipske i genotipske korelacije, kao i nedavno predložena nova klasifikacija OI.