Osteogenesis imperfecta: forensic assessment of traumatic injuries. Case report and literature review

Hostiuc Sorin*, Căpățînă Cornel, Curcă G. Cristian, Picioruș Iuliana

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Abstract: A 39 years old male with osteogenesis imperfecta type I presented to an emergency clinic accusing pain and movement limitations in his left arm appeared after a traumatic event. Clinical and radiological examinations revealed a fracture of the distal end of his left humerus, but also an underlying pathologic condition: osteogenesis imperfecta. Osteogenesis imperfecta patients may represent a challenge for forensic evaluation, particularly when trying to differentiate between spontaneous and traumatic fractures. Most of the recent published data regarding osteogenesis imperfecta focused mainly on the association or differential diagnosis with battered children syndrome. The authors review the particularities of adult OI and the possible pitfalls in medical legal interpretation.

Key words: osteogenesis imperfecta, Lobstein disease, forensic, legal medicine, battered children syndrome, fractures

Osteogenesis Imperfecta (glass bone disease [1], Lobstein disease [2], blue sclera disease, brittle bone disease, Porak and Durante disease [3]) is a clinical heterogenic entity characterized by increased bone fragility due to qualitative and/or quantitative collagen metabolism anomalies; bones have abnormal osteoblasts, a decreased bone mass, an anomaly regarding caveous-lamellar bone transition. Severity varies greatly from lethal intrauterine forms to mild ones, with a normal life span and only slightly increased fracture risk.

Classification and main clinical findings

The most used up to now classification is the one made by Sillence, based mostly on clinical and radiological findings, the genetics of the disease having at that time many unknowns [4], [5]; he classified it into four main types: I - the mildest and most frequent form, II – usually lethal in neonates, III and IV – intermediate types; this classification was completed by Glorieux, Rauch [6] and others, now being known eight main types and a some more OI-like syndromes. Type 1: has an autosomal dominant inheritance and is the most common (1:30000) and mild form, with a normal lifespan. Patients have variable bone fragility, moderate bone deformity, blue sclera, wormian bones, loose joints, poor muscle
tone, deafness, some degree of eye protrusion, scoliosis, kyphosis, and usually normal birth weight. Fractures are usually healing well but sometimes a hypertrophic callus can be found. Is further classified in [7]: in IA (less severe, without dentinogenesis imperfecta) and IB (more severe, with dentinogenesis imperfecta).

Type II is the most severe form (1:60000), usually lethal in the neonatal period. Clinically associates short limbs, often frog-legs, small chests, soft skulls, very dark or blue sclera, low birth weight, intrauterine fractures (skull, vertebrae, long bones), flat vertebral bodies, very short, telescoped femurs, beaded and short ribs, macrocephaly (rarely microcephaly).

Infants usually die within a few weeks up to a year after birth due to respiratory failure or intracerebral hemorrhage. They are further classified in: IIA (most severe, with broad and short long bones, broad and beaded ribs, grossly defective mineralization of the skull [8]), IIB (broad and short long bones, thin ribs with little or no beading) and IIC (thin and longer long bones, thin and beaded ribs, microcephaly, proptosis, white or slight blue sclera). Subtypes IIA and IIB have autosomal dominant inheritance, IIC a recessive one.

Type III is the most severe form (1:60000), usually lethal in the neonatal period. Clinically associates short limbs, often frog-legs, small chests, soft skulls, very dark or blue sclera, low birth weight, intrauterine fractures (skull, vertebrae, long bones), flat vertebral bodies, very short, telescoped femurs, beaded and short ribs, macrocephaly (rarely microcephaly).

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Type IV has an autosomal dominant inheritance. Clinically is moderately deforming with less severe phenotypical appearance compared to type III with moderate to severe growth retardation, long bones bowing (in a lesser extent than OI III), low height for age, short femur and humerus, ligament laxity, scoliosis, vertebral compression, white sclera, sometimes dentinogenesis imperfecta [9] upon which is subclassified in IVA (without) and IVB(with).

Type V has an autosomal dominant inheritance. Clinically has a moderate severity, having as characteristic lesions hypertrophic calluses at fracture sites (also can arise spontaneously) and interosseous membrane ossifications (antebrachial membrane ossification leading to dislocation of the radial head [9] or lower leg membrane ossification with subsequent bony ankylosis of the lower leg [10]); other observed lesions manifestations were dystocia due to cephalopelvic disproportion secondary to hypertrophic callus formation in iliac bones [9] or brainstem and cerebellar hypoplasia [11].

Type VI is a moderate to severe form, clinically much similar to Type IV, probably transmitted autosomal recessive, with long bone deformity, coxa vara, protrusio acetabuli, vertebral compression fractures, osteopenia, bulbous metaphyses, ligament laxity, normal dentition and white or pale blue sclera.

Type VII was up until now only found in a group of Quebec Indians; it is characterized by the presence of multiple fractures at birth but with decreasing frequency throughout adulthood, slightly blue sclera, short stature, rhizomelia and coxa vara.

Type VIII was only found in 2007 by Cabral, has a recessive inheritance and the severity is very high, resembling OI Type II; it is characterized by severe osteoporosis, shortened long bones, soft skull with wide open fontanel, white sclerae, a round face, and a short barrel-shaped chest, vertebral compression fractures, long hands compared to the forearms, with long phalanges and short metacarpals [12].
Genetics

OI is determined by a collagen metabolism deficiency, either qualitative, quantitative or both [9]. Most known genotypes include mutant COL1A1 and COL1A2 [6], although some other genes are also involved, like CRTAP or LEPRE1; also, the genes responsible for some OI Types (V, VI, VII) are not yet identified, although it they were proven not to be associated with COL1A1 or COL1A2 genes [13, 14]. Collagens are a large super family characterized by a unique repeating Gly-X-Y motif required for the formation of the triple helical tertiary structure [15]. Mutations of the fibrillar collagen were among the first proven to be cause of OI due to COL1A1 and COL1A2 mutations [16].

The most well known COL1A1/2 mutations causing OI are: for type I: Functional null COL1A1 alleles [17] (a defect in splicing of the pre-mRNA of COL1A1 [18]; G-A transition in the first position of the splice donor site of intron 26 [19]; 5-bp deletion near the 3-prime end of one COL1A1 [20], etc) or synthesis of abnormal procollagen I: cysteine-glycine substitution in position 1017 in the telopeptide [21], glycine to cysteine substitution in position 94 [22]; for type II: glycine to cysteine substitution in COL1A1 in position 718 [22], 988 [23] deletion of about 500 bp in the pro-alpha-1(I) gene [24], etc; for type III: glycine to cysteine substitution in Col1A1 in position 526 [22], gly to arg substitution in position 154 [25]; homozygous gly to ser mutation in position 751 of the COL1A2 [26], gly to glu substitution in position 76 of the COL1A1 [27], glycine to tryptophan in position 277 of the proc2(I) collagen chain [28], etc; for type IV ser to gly substitution in position 832 [29] or arginine for glycine substitution in position 1012 for COL1A2 [30].

CRTAP (cartilage-associated protein) is necessary for efficient proline 3-hydroxilation in fibrillar collagen; homozygous mutations can cause recessive OI, ranging from mild (rhizomelic) Type VII form if 10% residual CRTAP is still present [15] to lethal, Type IIC OI in complete loss of CRTAP (homozygous single-base pair (T) deletion in exon 4 (879delT) [15]). LEPRE1 produces Prolyl 3-hydroxylase 1 (P3H1) that hydroxylates pro986 of type I alpha-1 chain by forming a complex with CRTAP and cyclophilin B; all known mutation led to premature termination codons and minimal mRNA and protein synthesis with decreased coPro966 hydroxylation and excess lysyl hydroxylation and glycosylation along the collagen helix; the patients were classified in Type VIII OI [12].

Laboratory and imaging studies

OI main Rx characteristic is generalized axial and appendicular osteoporosis. Long bones showing thin cortices, osteoporosis, multiple cystic areas, anterior and lateral bowing of the femur and anterior bowing of the tibia, codfish vertebra (vertebral compression between the cartilaginous disk spaces), and wormian bones are frequent findings.

Often large with periostal thickening calluses are found. Recent advances in OI treatment with bisphosphonates can lead to specific imaging findings - cyclical pamidronate treatment determines the appearance of sclerotic growth recovery lines in the long bones.

The diagnosis of OI is based on clinical and radiographic findings. There is no specific laboratory diagnostic test, although fibroblast cell culture can detect the collagen abnormality in 85% of OI patients [31]. The type of OI may need specific criteria either genetic (LEPRE1 mutations in Type VIII), histological (mesh-like lamellar pattern in Type V, "fish scale" in Type VI). The diagnosis is based on the presence/development of multiple pathologic fractures with callus formation and deformity; in their absence the initial Rx diagnosis may be difficult, especially with battered child syndrome.

Other imagery examinations may also be useful in OI diagnosis or management: CT (useful especially in basilar impression assessment, the evaluation of middle ear narrowing or
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Otosclerosis), MRI (basilar impression with associated spinal cord compression, syringohydromelia, communicating hydrocephalus), prenatal ultrasound (OI can be diagnosed from week 17 by detecting morphologic bone anomalies like decreased calvarium echoes with supervisualized intracranial structures, long bones diminished length, bowing and angulations, multiple rib fractures, etc)[32].

Treatment

OI patients may present a wide range of deformities and associated conditions (neurological disorders, dental problems, ocular anomalies, constipation, swallowing and respiratory problems, etc; some of them can be treated pathogenically by various methods summarized in table 1.

Dietary

<table>
<thead>
<tr>
<th>Dietary</th>
<th>Vitamin D and Calcium Supplements</th>
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<tbody>
<tr>
<td>Medical</td>
<td>Biophosphonates (esp. pamidronate) Can increase bone density and diminish the fracture rate and the pain</td>
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<tr>
<td></td>
<td>Growth hormone Controversial, used sometimes for stature increase</td>
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<td>Symptomatic Esp. analgesics for pain management</td>
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Orthoses and other mobility aids

| Orthoses and other mobility aids | Wheelchairs, ankle/foot orthoses in extreme cases of ligament laxity, spinal braces, etc. |

Surgical

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<th>Surgical</th>
<th>Soft tissue Can relieve lower limb contractures</th>
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<td></td>
<td>Bone The most used is intramedullar stabilization with or without osteotomies.</td>
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New treatment options

| New treatment options | Fetal mesenchymal stem-cell graft in bone after in utero transplantation[33] |

Table 1

Minimally displaced fractures can be treated with cast immobilization and careful follow-up only if satisfactory reduction with minimal subsequent mobility is possible to achieve; if not or significant displacement is found surgical treatment is the best option. The preferred internal fixation methods are those using load-sharing device like intramedullar rods (both fixed length and extensible Bailey Dubow rods); plates and screws must be avoided as much as possible.

Usually OI fractures heal at a relatively normal rate in most patients [34]; there is though a higher complications frequency like nonunion, joint penetration, fracture at the rod tip, fixation device migration, loosening of components of extensible rods, often associated with incorrect fracture management; for example a history of inadequate treatment of the initial fracture was seen in 50% of non-unions [31].

Case presentation

A 39 years old male with OI Type I presents to the Hospital with pain and left arm functional impotence secondary to an aggression (hit with a bat over the left arm). Clinical examination revealed left arm pain at passive and active mobilization, clicks at passive mobilization and blue sclera (fig 1). Radiological examination revealed increased osteoporosis (humeral distal epiphysis, cubital and radial proximal epiphysis, elbow articulation deformity, exostoses, thinner cortical bones, and a minimally displaced, transversal supracondilar fracture of the left humerus (fig 2), treated with cast immobilization for a month and a half.

Fig. 1 Blue sclera associated with Lobstein disease
Hearing evaluation showed medium mixed (predominant transmission) hearing loss at the right ear. Final diagnosis was: left humerus supracondilar fracture and Lobstein disease. Two weeks after was performed a medical-legal examination that confirmed the traumatic lesions, the mechanism of productions and assessed the gravity.

**Fig. 2** Radiological aspects in Osteogenesis imperfecta

**Discussions**

OI poses two major problems from a medical-legal point of view: the first is related to the differential diagnosis with battered children syndrome and the second with interpreting the effect of a traumatic lesion to a patient with this disease.

1. Bone fracture are amongst the most frequent manifestations of battered children syndrome after soft skin lesions [35]; often found in battered children syndrome are metaphyseal, sternal, scapular, posterior costal, and spinous processes fractures [36, 39] Differential diagnosis between them has a crucial importance in these cases as the misinterpretation may lead to major psychological, social, medical and judicial complications [37, 40]; an association between BCS and OI is also possible – we must keep in mind in these cases that usually the frequency of bone fractures in children with OI decreases rapidly after 1 year – subsequently, any fracture after this age must be regarded very carefully [38]. If the victim is not known with OI there may be difficulties with the differential diagnosis with other osteopenic syndromes like bone cysts, osteolithic neoplasies, osteoporosis or diseases associated with the development of hypertrophuc calluses (some primary bony or cartilaginous syndromes).
2. The interpretation of found traumatic lesions to a OI patient must reach the following aspects:
   • intensity of the traumatic act: a low intensity traumatic act can determine one or even more fractures; also these can appear during normal physical acts like walking or even spontaneously in bed, especially in lower skeleton; very useful in confirming the violent nature of a fracture is the presence of another traumatic marks near the fracture site. In our case they weren’t found as the traumatic event happened two weeks earlier, nor were noted in none of the hospital papers - these could suggest a lower intensity traumatic event and are posing difficulties regarding the mechanism (was he hit with a blunt object? Did he fell on his hand?). The fact that the fracture site in relatively transverse and also it’s positioning could suggest it was produced by hitting the victim with a blunt object.
   • needed time to heal: patients with OI have healing times not signoficantly different from normal persons; some surgeons prefer though a longer immobilisation as the complications rate is increased.
   • complications that may appear are more frequent and sometimes have specific characteristics (see above); they can determine an increase in day-care number. In cases where they arise it also must be analysed the surgical management, as up to 50% are iatrogenic.
   • prolonged immobilisation may lead to articular stiffness or local pain more frequent than in normal patients – this theoretically could lead to an increase in day-care number; in their evaluation one must keep in mind that frequently the cause – hypertrophic calluses usually is preexistent and it’s manifestations articular stiffness and pain may not be necesarly associated with the fracture but the disease itself.

Conclusions

OI, by altering the bone, both qualitatively and quantitatively, may lead to increased difficulties in the medical-legal interpretation of traumatic lesions. To increase the accuracy of the forensic evaluation, personal medical data from before the traumatic event should be scrutinized. The patient must be carefully followed during the healing process and any anomalies/complications must be noted and analyzed until complete healing. Soft tissue associated traumatic marks may prove very useful in evaluating the kinetic energy associated with the traumatic event.

References

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