REVIEW

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The Orthopaedic Assessment of Children with Osteogenesis Imperfecta

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ABSTRACT

Osteogenesis Imperfecta (OI) is an inherited skeletal dysplasia characterized from bone fragility and skeletal deformities. OI presents with heterogenous features and variability in severity. Multiple systems are affected, since the disease involves the synthesis of collagen type I. Diagnosis is mainly based on the incidence of fractures. Severe osteoporosis, repeated fractures and fragility affect the skeleton and severe deformities are the result. Spine deformities are common. Muscle function and mobility is affected. Medical treatments including biphosphonates, denosumab, TGFb inhibitors are reported to increase bone mass, but fractures remain the main consideration of OI. Surgical treatment with the use of intramedullary expanding rods increases bone strength, correct deformities and provide stability for the mobilization of the affected patients. These procedures have a high rate of complications but have significantly improved the quality of life of the affected children.

KEYWORDS: Osteogenesis ; Imperfecta

Definition

Osteogenesis imperfect (OI) is a rare bone dysplasia, covering a broad area of connective tissue disorders that is characterized from bone fragility, fractures and bone deformities. It is estimated with an incidence of 1/ 15000 live births. In our area in north of Greece, we have 6 children with OI under our orthopaedic care.

OI is due to mutations in the genes that are responsible for the synthesis of the chains of the type 1 collagen. Osteoblasts appear primarily affected. Increased function of TGFb (Transforming Growth Factor beta) signalling that exhibit increased bone turnover and low bone mass, is found. Initially lesions in chromosomes 17 and 7 affecting COL1A1 and COL1A2 where identified, but today there is an increasing number of involved genes. We have described a new mutation in a severely affected girl with OI. The mutation is an autosomal dominant one but may appear as recessive or X-linked disorder. More than 50% of cases are new mutations. This is clinically important regarding the proper assessment of relatives for children affected from OI. [1-8]

Diagnosis

Diagnosis is mainly based on the feature of bone

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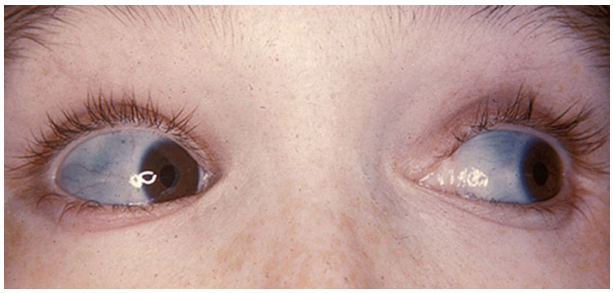

Figure 1: *Blue sclera of a patient with OI*

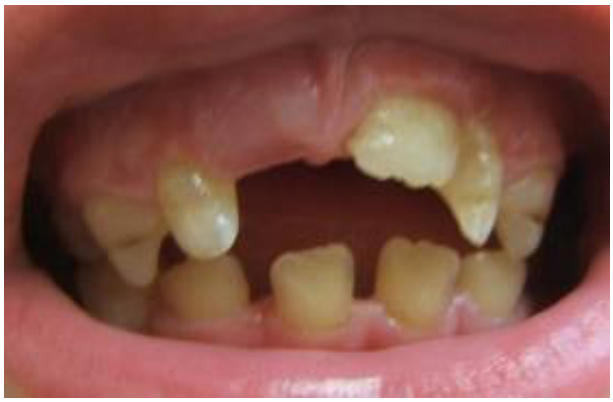

Figure 2: *Severely affected teeth in a patient with OI*

fragility. There are characteristic radiological elements of osteoporosis and alterations of bone morphology but are not unique for OI. Biochemistry bone measurements and bone mineral density measurements are helpful. Clinical picture with extra skeletal manifestations add to the accuracy of the diagnosis. Fractures of long bones, with minimal violence remain the main feature for the diagnosis of OI. Transverse type of fracture in the diaphysis of a long bone is the most typical pattern of a fragility fracture. [1,2,9,10]

Classification

Classification of a disease with a wide variety of clinical presentation is difficult. Initial classification was proposed from Silence, in four types, according to the severity of clinical and radiological manifestations. Type I was the no deforming type of OI characterized from blue sclera. Type II was the lethal perinatal OI, presenting with prenatal fractures and short life expectancy. Type III was the severe progressive type with deformities and multiple fractures. Type IV was described as a moderate form with less incidence of fractures and mild deformities.

Recent progress in genetics of OI has created a tendency to classify OI according to genetic defects. There is no correlation between the genotype and phenotype presentation of the disease. Mutations in the genes affect collagen structure either as an amount of pathological collagen either as changes in the structure of type I collagen. Genetic analysis of the OI cannot be linked with the clinical picture of OI.

Today Silence classification is used, while a 5th type of OI was added, characterized from calcification of the interosseous membrane of the forearm. [10-14]

Clinical Manifestations

OI is characterised from bone fragility, in all types of the disease. Since the genetic lesion affects the collagen structure, many clinical manifestations in almost all the human organs, may appear.

OI **type 1** has bleu sclera. Fractures are rare at birth but there is an increase in number, as the child grows. Usually, they are transverse fractures of long bones. Deformities are rare. There is decreased bone mass. Fractures are rare in vertebrae.

On **type 2**, short and deformed long bones appear in the prenatal ultrasonography. Reduced length of the femur is the most reliable parameter to detect skeletal dysplasia. Rib fractures are observed in uterus. The vast majority of patients die in the first month of life. Decreased ossification of the skull and the facial bones is found.

Type 3 OI is the most severe type, with multiple fractures and severe deformities of the long bones. Fractures appear from birth. Children have short stature. Growth plate appears elongated, leading in short bones. There are problems with dentinogenesis. Vertebral fractures may be found. Children present problems with scoliosis. Blue sclera is found and occasionally there is an increase of the intensity of the coloring, before fractures. As OI is a collagen disease there are several clinical manifestations. There is increased ligamentous

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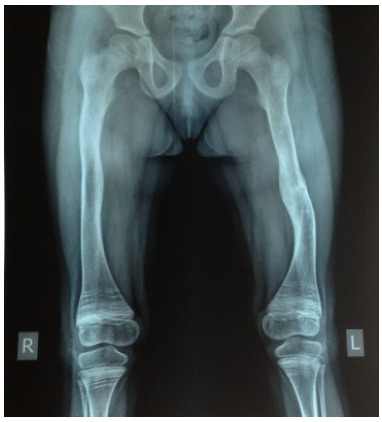

Figure 3: *Thin cortices and osteoporotic long bones, with a healed fracture of the left femur*

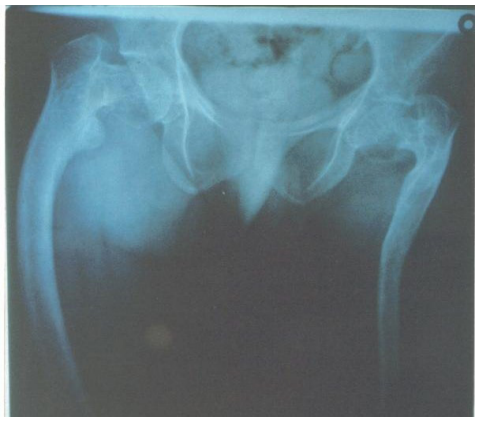

Figure 4: *Deformed femora and protrusion of the left acetabulum, with thin cortices*

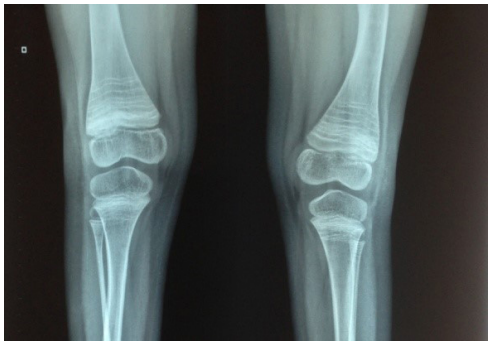

Figure 5: *Zebra lines in the metaphysic of the long bones*

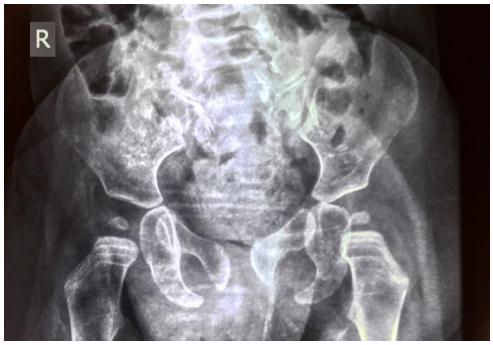

Figure 6: *Zebra lines in the metaphysis of the femur*

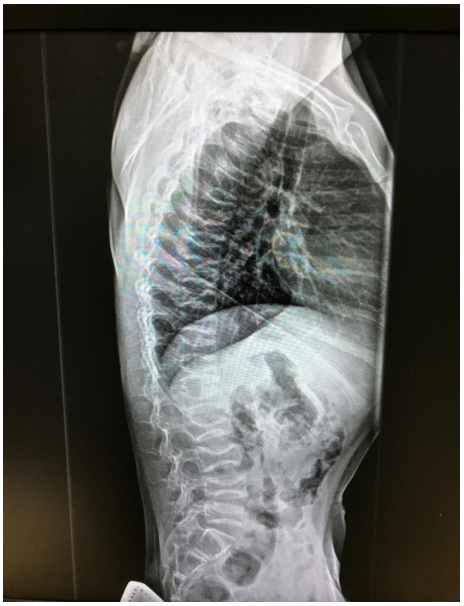

Figure 7: *Severe osteoporosis of the vertebrae that are markedly biconcave in shape.*

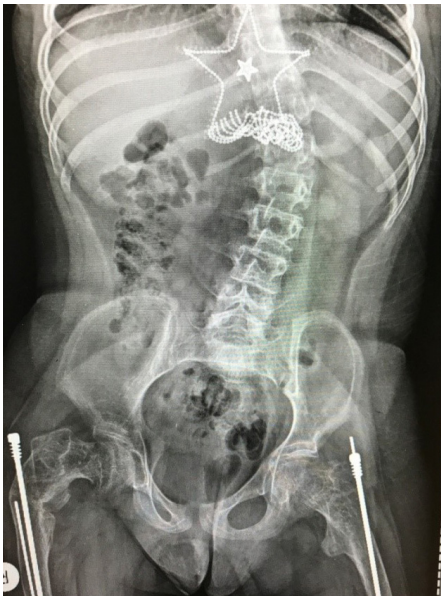

Figure 8: *Scoliosis in a child with OI*

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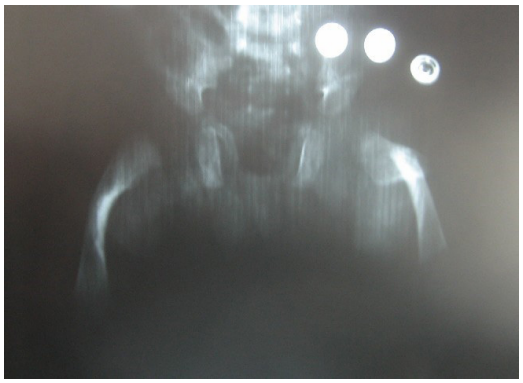

Figure 9: *Neonatal fracture of the left femur in a girl with OI.*

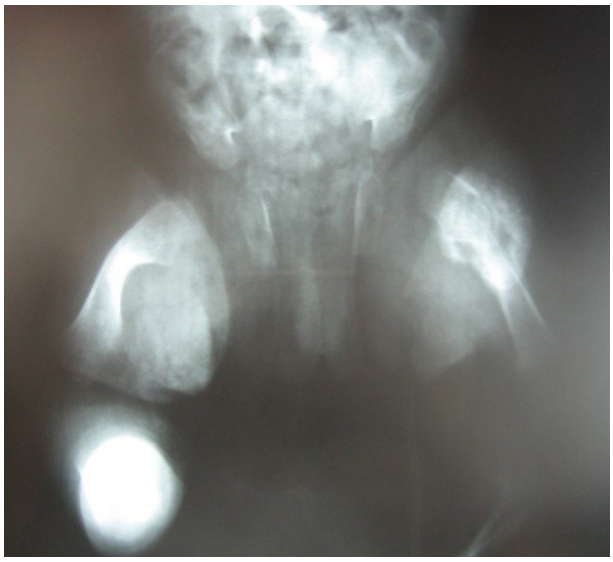

Figure 10: *Callus formation of the fractured left femur, deformity of the right femur*

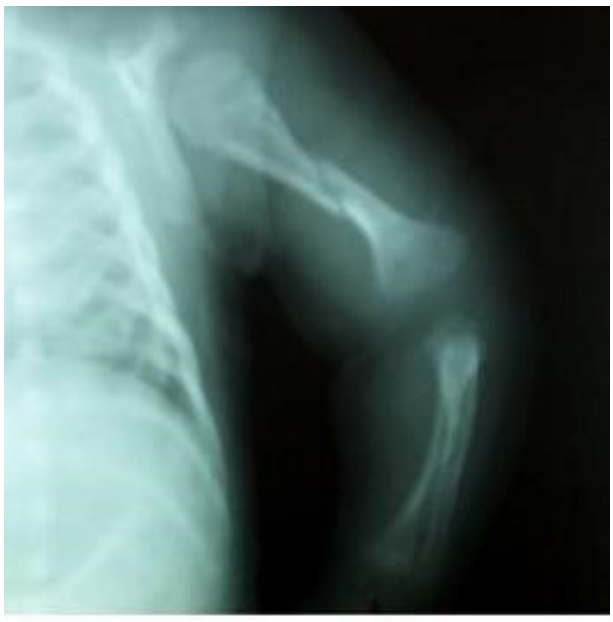

Figure 11: *Fracture of the humerus, as the first fracture of a neonate with OI*

laxity. The head has a frontal prominence and there is an ageing appearance, the patient looks old. Craniofacial structures appear abnormal. Hearing problems are common. Children have normal intelligence.

Type 4 has a mild form of the disease. There are frequent fractures, but less severe deformities. Blue sclera is absent.

Type 5 had increasing ossification of the intraosseous forearm membrane. [1,2,10-14]

Radiology

Severe osteoporosis is the main characteristic. Cortices are thin. Severe deformities appear with almost complete bending of the long bones, similar to semicircle. There is thinning of the cortices with reduced width of the intramedullary canal.

Protrusion of acetabulum may appear later. Vertebrae have a characteristic biconcave shape, leading further to scoliosis. A most prominent sign is the zebra line phenomenon that is seen in children with OI, no matter whether they are under treatment for the osteoporosis. Bone mass index remains in low prices, in OI. [1,2,10]

Neonatal fracture

A neonatal fracture of a long bone may be the initial manifestation of OI. The severe lethal type 2 OI may appear on prenatal screening with bowing of femora and reduced length of the femur. The fracture is found in an uncomplicated normal delivery. On radiological examination apart from the fracture, the cortices are thinned and deformed. Fractures usually affect the femur and the humerus but even fractures of the tibia, ribs or vertebrae have been reported. Treatment of the fractures follows the general principles for neonatal fracture, with skin traction (Gallow's traction) for the femur and appropriate splinting for the humerus. [15-18]

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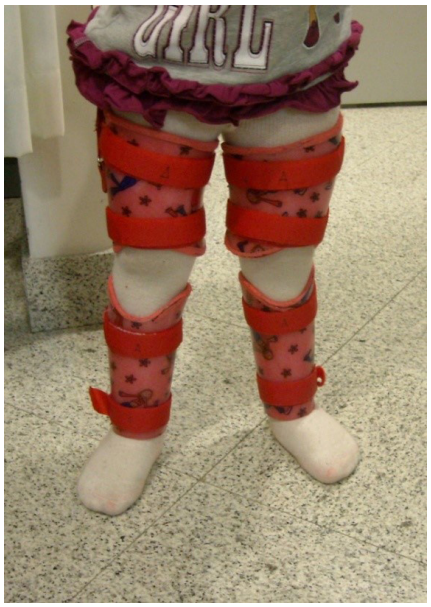
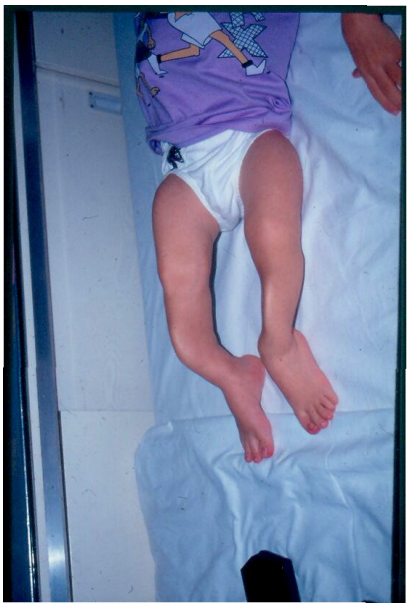


Figure 12: *Casts applied for protection in the preschool age, in a child with OI*



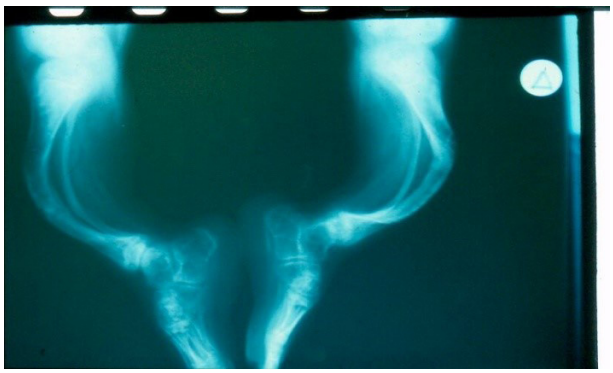


Figure 13, Figure 14: *Clinical picture and radiological image of a boy with severe type 3 OI. Note the semi-circular appearance of the tibiae.*

Deformities - Fractures

Repeated fractures and reduced bone strength lead in severe deformities of the long bones. Even in supported passive standing position, the fragile long bones sustain deformities that lead in an almost circular shape of the femur or the tibia. Same deformities are found in the upper arm. The bone healing is not impaired but the callus formation consists from poor bone quality in OI. Refractures and delayed bone union are reported in OI. [11,19]

In the initial stage appropriate functional casts are used to protect the shape of the limbs and provide support for the children, in order to walk independently.

Spine Scoliosis

Lesions of the vertebrae are common in OI. Early vertebral fractures in the first years of life are among the initial findings of OI. Vertebrae appear on radiological assessment with severe osteoporosis, thinning of the cortices and biconcave shape. Scoliosis is a common finding in OI female children. Scoliosis is another cause of gait disturbance in cases of a spine that is out of balance. Use of custom-made cast with elasticity is initially used in order to reduce the increase of the curvature. Commonly used casts for the adolescent scoliosis that use pressure cannot be applied in children with OI. Surgical treatment of severe scoliosis in OI is a great challenge for the spine surgeon. Fixation of pedicle screws may require the use of cement. Spine fusion is impaired in those children that are under regular bisphosphonate treatment.

Atlantoaxial abnormalities have been reported as complications in children with OI. Radiological manifestations include basilar invagination or impression and platybasia. Neurological symptoms with weakness of the limbs must be investigated for craniocervical lesions with appropriate MRI

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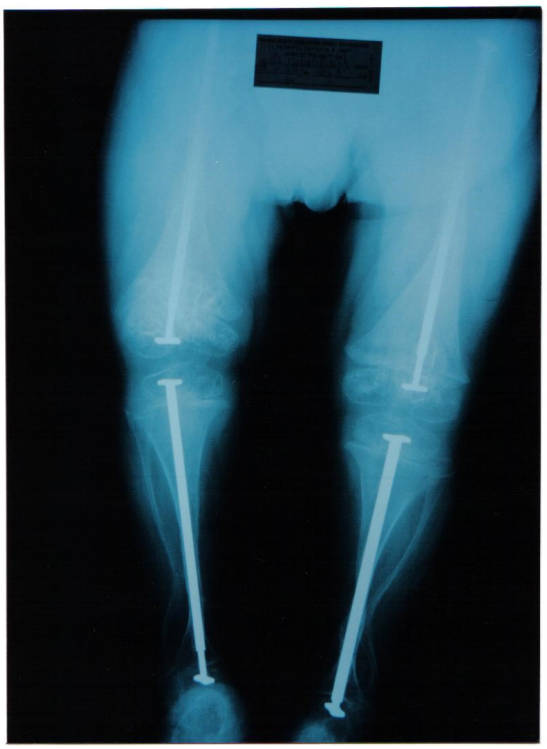


Figure 15: *Correction of both femur and tibia, with telescoping Sheffield rods, with multiple osteotomies. Impressive restoration of the axis of the lower limbs.*

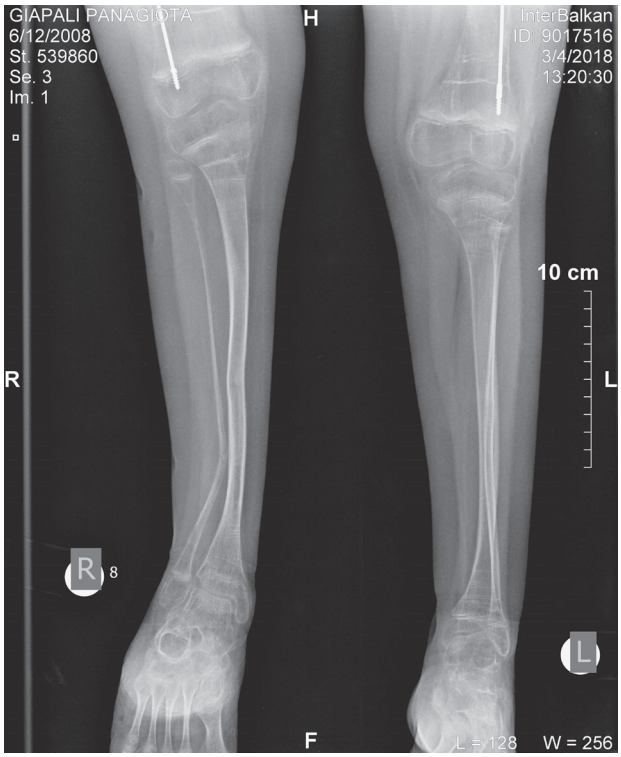
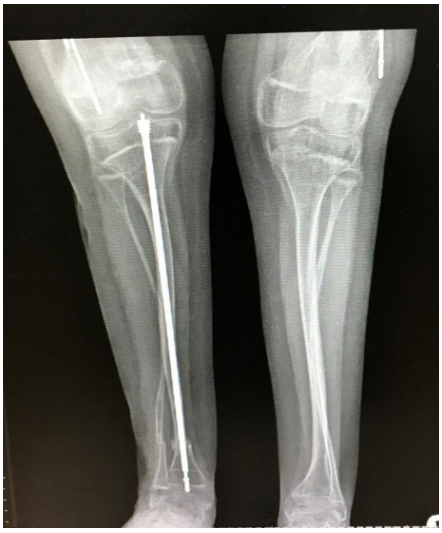


Figure 16: *Deformity of the right tibia, with delayed union of the transverse fracture of the tibia diaphysis. Notice the reduced width of the canal*



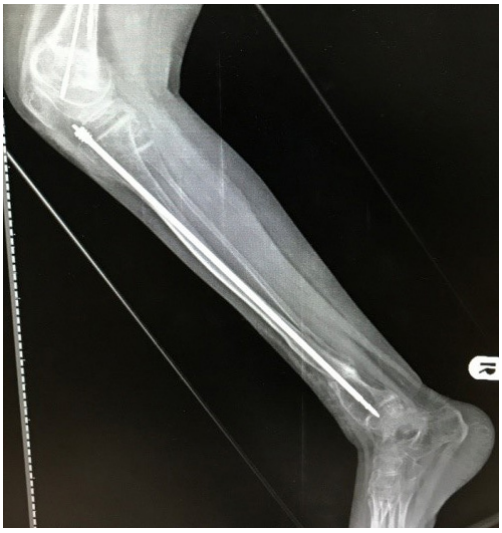


Figure 17, Figure 18: *X-ray examination AP and lateral of the corrected right tibia, with Fassier Duval expanding rods. Surgery performed the year 2018*

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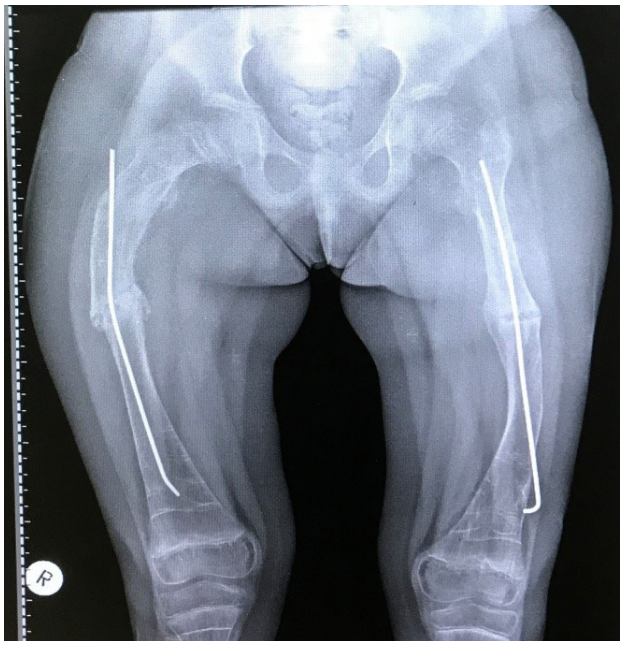

Figure 19: *Initial stabilization of fractured femur with intramedullary nails, year 2016*

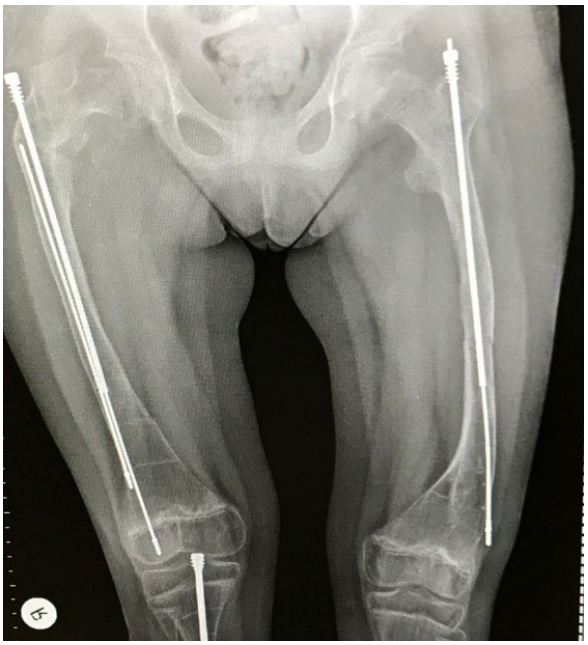

Figure 20: *repeated surgical stabilization with expanding rods Fassier Duval, year 2020*

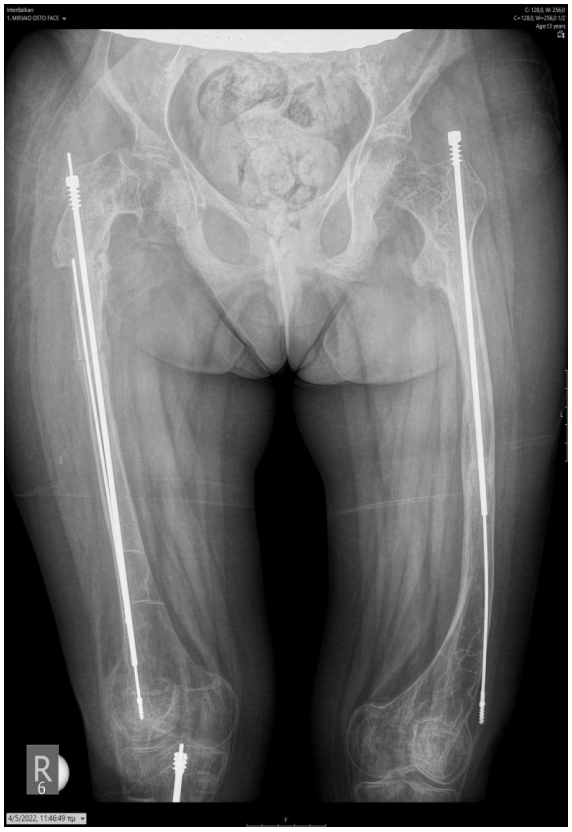

Figure 21: *Correction of recurrence of deformity of the right femur, with new osteotomy, on 2022*

evaluation. Regular assessment of the cervical spine in a year basis is recommended after the 6th year. Spondylolisthesis has been reported in OI children. [20-25]

Muscle Lesions

Muscle weakness is an important feature and gait disturbances with increased motor disability affect the patient, further adding to the difficulties from the bone deformities. Patients have reduced mass muscle and muscle function is impaired. Collagen type I is found in the tendons and ligaments and the disturbance of collagen synthesis affect the connective tissue. Tendon ruptures are found in OI. Children have decreased mobility; this is another factor predisposing to reduced muscle strength. It is important with appropriate physical therapy to keep children in standing and walking activities. Increased ligamentous laxity is a common feature in OI, leading in joint dislocation. [2,10,26,27]

Mobility

Children with OI type 3 are severely affected on their motor ability. Deformities of the upper and lower limbs are occasionally extremes and children

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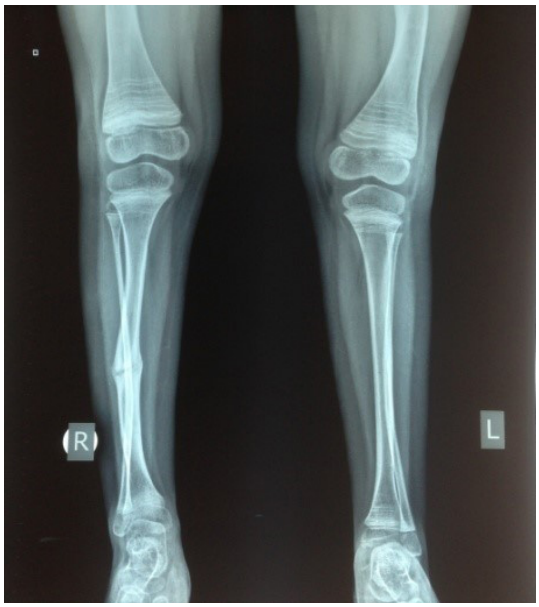


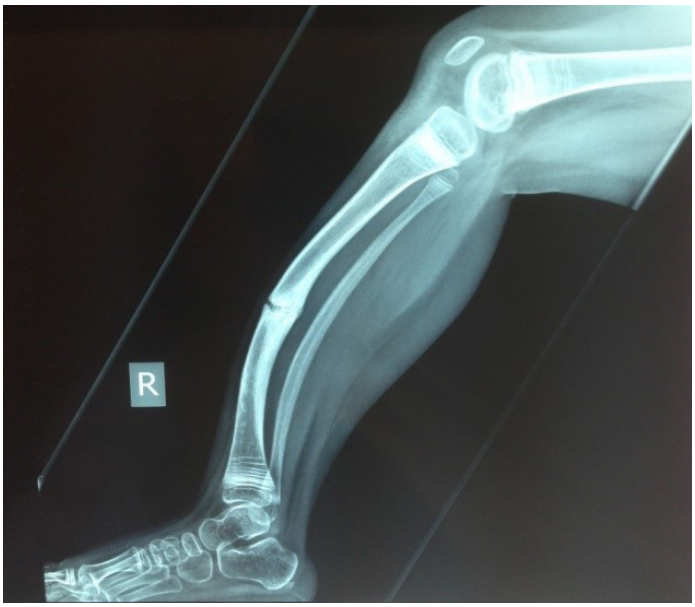
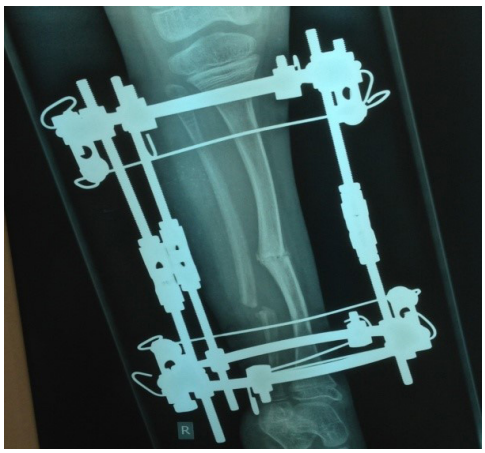


Figure 22, figure 23: *Anterior bowing and delayed union of the fracture of the right tibia, 2014*



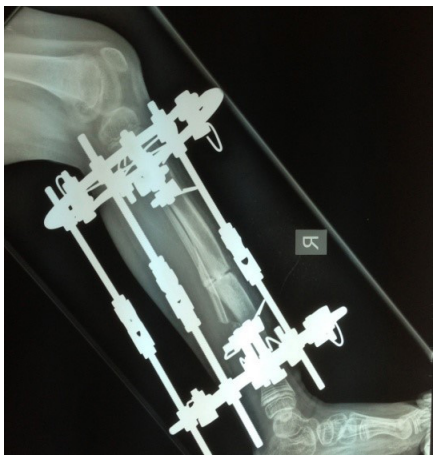


Figure 24, Figure 25: *Correction of the deformity, with application of Ilizarov device, 2014, note the osteotomy of the fibula.*

cannot achieve the upright position. Muscle weakness as already described is an important factor for the decreased mobility. Respiratory and cardiovascular deficit add to motor disturbance. [28,29]

Medical treatment

The standard care for paediatric patients is the use of bisphosphonates. Intravenous use increases the bone mass and reshaping of the vertebra has been found. The number of fractures is not significantly reduced and deformation of the long bones remains a severe problem.

Denosumab, and anti-RANKL antibody that act by inhibiting osteoclast differentiation is currently studying for OI in children. It has shown to improve bone mineral density. There is a risk of increased hypercalcemia.

The use of sclerostin inhibition and TGF beta inhibition are reported with promising results. Anabolic agents as teriparatide have been also used, but it was not effective in severe forms of OI. Progenitor cell therapy, with transplantation of healthy stem cells, has been recently reported. [30-37]

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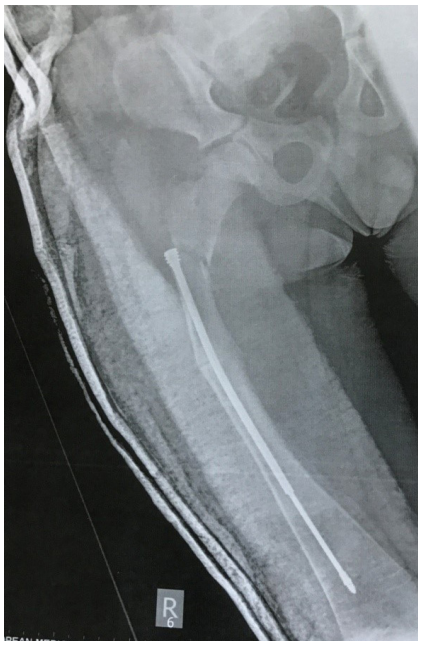

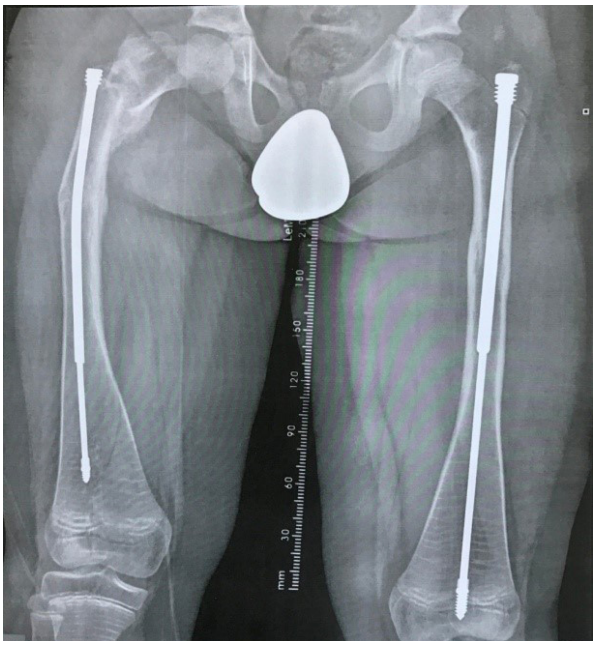

Figure 26, Figure 27: *Fracture in the subtrochanteric region, just above the rod. Treatment with immobilization in a spica and union of the fracture*

Surgical treatment

Surgical treatment is an essential part for the management of the children with OI. The aim of surgery is to straighten a deformed bone, providing adequate support in order to sustain appropriate loading during the standing and walking phase. The development of the expanding rods (Fassier Duval) has completely altered our approach for the surgical management of OI. Rods can support the weak bone in order to reduce the incidence of fractures and provide adequate support for preventing displacement of the fractured bone. Early surgery can prevent severe bone deformities.

Correction of deformities

Long bones appear as almost semi-circular shapes. In order to become straight several segmental osteotomies are required. Intramedullary canal is reduced in size and appropriate preoperative planning is required for the correct size of the rod. Longitudinal extensive incisions are required, with careful periosteal elevation and several segmental osteotomies. In the severe type 3 OI the feeling of the cortical bone is like trying fixing pieces of sand. Expanding rods are secured in the epiphysis of the bones, enabling the introduction of the male in the female part of the system. As the child grows, the telescoping rods are elongating.

Osteotomies can be performed subcutaneously, under image intensifier, with controlled type of osteotomies. Preoperative planning can be performed today threw a computer assisted method, in order to achieve accurate correction of the deformities. [38-44]

Severe deformities are mainly affecting the femur and tibia. But similar deformities affecting the humerus can be surgically treated with multiple osteotomies and rodding. [45,46]

In older children, locking plates with unicortical screw fixation have been recently reported, in cases with delayed union or pseudoarthrosis of the osteotomy.[47]

Tibia -Illizarov - Rods

Use of Ilizarov device is well established method for correction of deformities, with immediate weight bearing. Fixation of the wires in a bone with severe osteoporosis can be a problem in the use of the device. Leg lengthening procedure with Ilizarov

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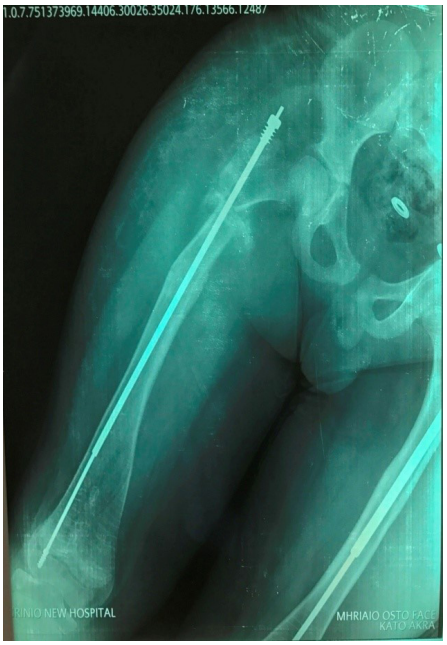
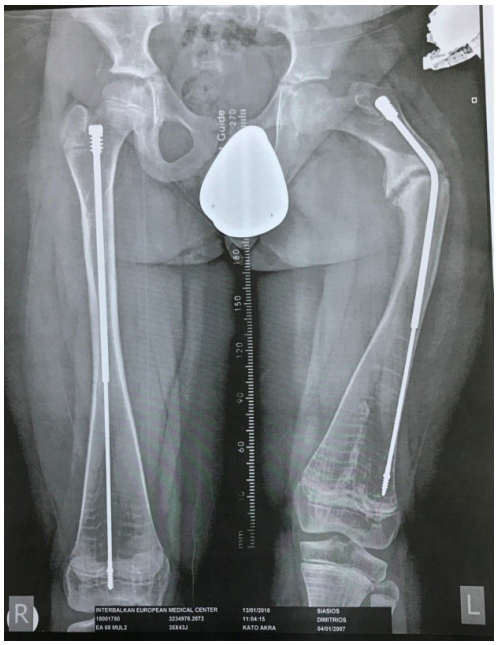


Figure 28: *Surgical correction after the union of the fracture, with subtrochanteric osteotomy and application of a new expanding rod Fassier Duval.*

device may encounter problems with the fixation of the wires and the stability. We have used the Ilizarov device for the accurate correction and stabilization of the deformity of the tibia that presented with a transverse fracture in the diaphysis. Bone healing was delayed as was expected in the fracture in the diaphysis of the tibia and not because of the underlying OI. Union was achieved and the device was removed. But the deformity recurred with further transverse fragility fractures and we treated the patient with the use of expanding rod (Fassier Duval)

Complications

Children with OI, even in milder forms as type 4, continue to sustain fractures, despite surgical stabilization with rods and appropriate medical treatment. Minimal activities or even absence of trauma, just as children are standing or walking, may trigger the fracture. Clinical signs of pain of the femur or cortical thickening occasionally are prenominal features for the fracture, similar to the atypical femoral fractures that are reported in anti-osteoporotic treatment. The presence of the rod acts



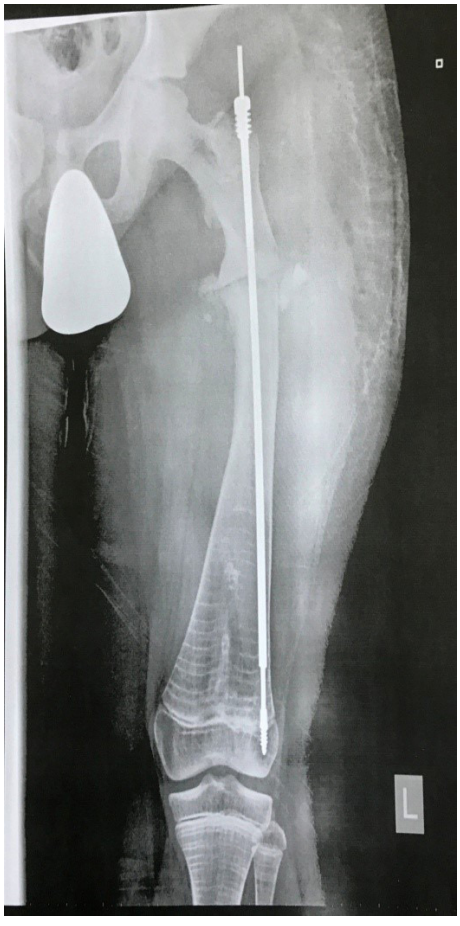


Figure 29, figure 30: *Pseudoarthrosis of the osteotomy of the left femur, with bending of the rod. Surgical treatment with realignment of the femur and insertion of a new rod.*

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as an internal splinting, reducing the angulation of the femur and treatment with appropriate bed rest is adequate for the healing of the fracture, and since the fracture healing is not impaired in OI. Fractures may appear in the top of the rod, leading to varus deformation and bend of the rod. Treatment provided was the revision of the rodding, with adequate subtrochanteric osteotomy, in order to re-establish the axis of the femur. Another patient presented with bending of the rod and delayed union and was treated with open procedure with removal of the rod, reduction of the femur and insertion of a new expanding rod.

There is concern regarding the union of osteotomies and fractures in children that are treated with bisphosphonates. We have used a period of drug vacancy of 3 months for those that are scheduled for an elective procedure. We are using osteotomes instead of power saw in order to reduce the heat necrosis of the bone. In those treated in emergency for the fracture, we discontinue the use of bisphosphonates for 6 months. [48-52]

Blood loss

Patients with osteogenesis imperfecta (OI) have been reported to be at risk for significant surgical bleeding, secondary to abnormalities in platelet function. The younger patients are at increased risk. Increased number of osteotomies may lead to severe blood loss. It is important to secure blood units before the surgical procedures. With minimal surgical incisions and minimal periosteal elevation, femoral rodding can be performed without excessive blood loss. [53]

Conclusions

Surgical treatment must be considered as an early procedure in young children, with the severe form of OI, in order to prevent severe deformities. The increasing number of fractures is an indication for surgical intervention. The mobility status of a young patient can be reserved with early intervention, since the straight bones that are increased in strength with the rod, can permit their independent walking. Surgical treatment with expanding rods is a procedure that can improve the mobility of children with significant deformities. There is a high rate of revision procedures, reported up to 50% of patients. This is mainly related to the growth of the young patients, repeated fractures and migration of the rods. [41-43]

Individuals with severe type III OI, are more often treated with intramedullary rods, simultaneously in both lower limbs and present improvement in their mobility. With appropriate orthotics they can become independent ambulators.

Severe types of OI are associated with severe mobility disorder, as already reported. But appropriate medical and surgical treatment can improve the quality of life of the patient and the family. Genetic interference is expected to further improve the status of OI.

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