The Orthopaedic manifestations of Osteogenesis Imperfecta: A Collective Review

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Abstract

Osteogenesis imperfecta (OI), or brittle bone disease, is a debilitating genetic disorder of connective tissue which is characterized by reduced skeletal mass and bone fragility. OI results from mutations in genes encoding for type I collagen. Since collagen is the major structural protein in bone, ligaments, tendons, skin, sclera and dentin, clinical manifestations of OI include fragile bones with skeletal deformity, blue sclerae, hearing loss, and opalescent teeth.

The orthopedic manifestations of OI are diverse. Most OI patients present with long bone fractures, joint contractures, foot deformities and bowing of long bones. Successful treatment of this condition is potentially challenging and requires a multidisciplinary approach. Surgical intervention is cumbersome because of growing bone, poor bone quality and soft tissue contractures. Advances in the medical management of OI have shown promising increases in bone mineral density and decreases in fracture incidence.

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Introduction

Osteogenesis imperfecta (OI), or brittle bone disease, is a debilitating genetic disorder of connective tissue which is characterized by reduced skeletal mass and bone fragility.[1] In contrast to osteomalacia, patients do not have disturbances in serum calcium and vitamin D levels. OI results from mutations in genes encoding for type 1 collagen which leads to formation of defective collagen. Since collagen is the major structural protein in bone, ligaments, tendons, skin, sclera and dentin, clinical manifestations of OI include fragile bones with skeletal deformity, blue sclerae, hearing loss, and opalescent teeth (dentinogenesis imperfecta).[2] Less severe manifestations of OI include generalized ligamentous laxity, hernias, bruising tendency, and excessive sweating.

Orthopedic manifestations of OI are diverse. Most patients with OI present with long bone fractures, joint contractures, foot deformities and bowing of long bones. They may have repetitive fractures which heal normally,[3] although Cheung and Ramirez have reported hypertrophic callus formation and delayed healing in some patients.[4-5] The aim of this thesis is to review the epidemiology, genetics, classification, clinical and radiological manifestations, and management of OI.

Epidemiology and genetics

OI has a prevalence of 1 in 15,000 children with wide variations in its phenotype.[6] It is caused by mutation of either of the two chains that form type 1 collagen, the major structural protein of the extracellular matrix of bone, skin and tendons.[7-8] The family of collagens is large and multivariable, each with their own different genes, structure and tissue distribution, and all with repetitive lengths. A collagen type 1 molecule consists of three polypeptide chains (two alpha 1 and one alpha 2 chains) that intertwine via a glycine residue at every third position, forming a triple-helical heteropolymer. Type 1 is the major fibrillar collagen, molecules of which cross-link to form fibrils and fibres of considerable length.[9-10] Most cases of OI are caused by an autosomal dominant genetic mutation, and in about 90% this involves one or two of the genes that encode the α-chains of collagen type 1 (COL1A1 and COL1A2). These genes are located on chromosomes 17 and 7.[11-12] Skyes describes two distinct categories of mutations.[13]

a. 'Excluded' type results in exclusion of the product of the mutant allele from the mature collagen molecule (non-deforming OI)
b. 'Included' type that permits the incorporation of a structurally abnormal chain (deforming OI)

Classification systems of Osteogenesis imperfecta

In 1906, Looser classified OI into two forms, congenita or tarda, depending on the severity of presentation.[14] Infants with OI congenita have multiple fractures in utero, whereas in individuals with OI tarda, fractures often occur shortly after birth or later.

Seedorf further subclassified OI tarda into two types: tarda gravis, in which the first fracture occurs in the first year of life, and tarda levis, in which the first fracture occurs after the first year of life,[15] although this classification has since been superseded. Hanscom and Winter proposed a classification system (1992) based on the dynamic nature of eight radiographic changes (Table I).[16]

i. Appearance of the diaphyseal cortex
ii. Degree of tapering of the long bones
iii. Platyspondylosis and biconcave vertebrae
iv. Time of closure of the distal femoral and proximal tibial epiphyses
v. Presence of chest wall deformity
vi. Trefoil-shaped pelvis and protrusio acetabuli
vii. Cystic changes in the epiphysis and metaphysis at the knee
viii. Ratio of femoral to tibial metaphyseal width (metaphysis measured at widest point)

Sillence classification

The most widely used OI classification system is proposed by Sillence et al.(1979), with types 1–4 based on clinical and radiological findings of skeletal deformities combined with genetic data.[17] Recently a new group of patients has been identified at the clinical and molecular level and added to the present classification as OI types 5-7 (Table II).[18-20]

Type 1 OI

A non-deforming type, patients are of normal or low-normal height and they usually do not have limb deformities. The clinical hallmark of type 1 OI is bony fragility and often multiple fractures during childhood. Fractures become less common after puberty. Blue sclerae are present at birth. Kuurila and Imani in several studies have shown that around fifty percent of these patients develop presenile deafness which usually develops in the third decade of life and therefore is not observed in children.[21, 22, 23] Fracture patterns include spiral and transverse fractures of long bones, particularly in the lower extremity. Avulsion-type fractures, such as olecranon and patellar fractures are common and are related to the decreased tensile strength of the bone because of low collagen content.[24] Type 1 OI does not affect longevity but influences morbidity due to recurrent fractures and complications as malunion and subsequent angular deformities of long bones.

Type 2 OI

A lethal type and the most severe form of OI. Infants with type 2 OI die at or shortly after birth. They are born with crumpled femora and ribs which are accompanied by severe kyphoscoliosis and pulmonary hypoplasia, which usually leads to death. Narrow thoraces, short and deformed extremities with multiple fractures, and a typical frog-like position are the main features of this type. Central nervous system malformations and hemorrhages are common due to the markedly abnormal collagen. Survival beyond one year is very rare.[25]

Type 3 OI

Type 3 OI accounts for approximately 20% of all patients with OI. This is the most severe of the types that survive. These patients have relatively large skulls but under-developed facial bones, leading to a characteristic triangular appearance of the face. The sclerae are usually pale blue at birth, but become normal in color by puberty. Patients are short in stature, with severe limb deformities including bowing of long bones and coxa vara.

Glorieux et al. have demonstrated that the characteristic popcorn appearance of the epiphysis and metaphysis which occurs in early childhood is caused by distortion of the growth plate, with zones of partially calcified cartilage and broadening of the epiphysis (Figure 1). These patients have poor muscle strength and muscular balance, and many use wheelchairs for mobility, or require walking aids.[26] Widmann has described the relationship of spinal deformities and pulmonary compromise in patients with type 3 OI during anaesthetic interventions.[27] Lumbar vertebral pedicles are elongated, leading to spondylolisthesis at the lumbosacral junctions.[28] The vertebrae are wedged and may assume a codfish-like biconcave morphology. Basilar invagination of the skull due to odontoid peg fracture and subsequent instability can present with headache, lower cranial nerve palsy, dysphagia, limb hyperreflexia, nystagmus, hearing loss, or quadriparesis.[29]

Type 4 OI

Patients with type 4 OI have a relatively moderate clinical presentation. Most have short stature with bowing of long bones and vertebral fractures. Inspite of multiple fractures in childhood with subsequent deformities, most patients are ambulatory. There is a wide age range for the first fracture and number of subsequent fractures in these patients. Dentinogenesis imperfecta may or may not be present in these patients. The sclerae are typically white.[30-31]

Type 5 OI

OI Type 5 is moderate in severity. It is similar to type 4 in terms of frequency of fractures and the degree of skeletal deformity. The most characteristic feature of this type is large, hypertrophic callus formation in the long bones at fracture sites and surgical procedure sites. Calcification of the interosseous membrane between the radius and ulna restricts forearm rotation and may cause dislocation of the radial head.[31] Women with OI Type 5 anticipating pregnancy should be screened for hypertrophic callus in the iliac bone as it can act as an obstacle for passage of fetus during child birth.

Type 6 OI

OI type 6 is extremely rare. It is moderate in severity and similar in appearance and symptoms to OI type 6. This type is distinguished by a characteristic mineralization defect seen in biopsied bone. The mode of inheritance is probably recessive, but it has not yet been identified.[31]

Type 7 OI

Type 7 resembles OI type 4 in many aspects of appearance and symptoms. Some cases resemble OI type 2, except that infants have white sclerae, small heads and round faces. Short humeri and femora are common, as is short stature. Coxa vara and trefoil pelvis are seen. OI type 7 results from recessive inheritance of a mutation in the cartilage-associated protein gene (CRTAP).[30-31] Partial (10%) expression of CRTAP leads to moderate bone dysplasia. Total absence of CRTAP has been lethal in all identified cases.[30]

Type 8 OI

Cases of OI type 8 are similar to OI types 2 or 3 in appearance and symptoms except for white sclerae. OI type 8 is characterized by severe growth deficiency and extreme under-mineralization of the skeleton. It is caused by absence or severe deficiency of prolyl 3-hydroxylase activity due to mutations in the LEPRE1 (prolyl 3-hydroxylase 1) gene.[30-31]

Differential diagnosis

The differential diagnosis for suspected OI depends on the severity of the condition and on the age of presentation. The condition can manifest in a variety of ways, and the differential diagnosis can be categorized into prenatal / neonatal, preschool and adolescence stages.[32]

Ramachandran differentiates OI according to age of presentation.[33] Conditions which should be suspected in the prenatal/neonatal stage include chondrodysplasia punctata, chondroectodermal dysplasia, Jeune dystrophy hypophosphatasia and non-accidental injuries. These conditions share some similarities to osteogenesis

imperfecta. Patients with hypophosphatasia present with blue sclerae, fractures, and wide fontanelles. Hypophosphatasia is characterized by low serum alkaline phosphatase levels and, in the severe recessive form, skin dimples overlying Bowdler spurs located symmetrically on the midshaft of the fibula, ulna, and radius.

During preschool years conditions such as pyknodystosis, osteochondromatosis, and Hajdu-Cheney syndrome have to be considered. During adolescence, Maffucci syndrome mimics OI. Other conditions which should be differentiated are rickets, osteopetrosis, Bruck's syndrome, and congenital syphilis.

Child abuse resembling OI

The distinction between mild OI and non-accidental injury is sometimes very difficult, especially in early infancy. Mild OI without family history appears similar to non-accidental injury. However it must be kept in mind that the two conditions can also coexist. According to Glorieux, *"Pediatricians, orthopedists, emergency room physicians, and others who see children with fractures need to consider OI as a possible cause, particularly in cases involving multiple fractures or a family history of fractures."*[34]

Management of OI

The goals of the treatment in OI are to decrease pain, prevent fractures and improve mobility. Treatment depends on the severity of the disease and on the age of the patient. A treatment strategy incorporates a multidisciplinary team approach which includes the pediatrician, geneticist, orthopedic surgeon, physiotherapist, occupational therapist, worker and family.[35-36]

Mainstay of treatment

As per the National Institute of Health's guide to OI for pediatricians and family physicians, the treatment strategies are centered over behavioral and lifestyle modifications, rehabilitation to improve muscle strength, orthopedic surgery for

deformity correction, splinting for pain relief, adaptive equipment, ambulation aids and weight management.[34]

Behavioral and lifestyle modifications

Infants with OI are prone to fracture with trivial trauma, thus one of the most important aspects of treatment is gentle handling from infancy. As these patients grow, proper techniques for lifting, sitting and standing must be employed.
It is of utmost importance to modify the home and school environment such as keeping the floor free of obstacles that could cause an accident. Strenuous activities which could rotate the spine, and negatively impact on weak bowed long bones, should be avoided.[34]

Physiotherapy and rehabilitation

Physiotherapy, rehabilitation, and occupational therapy are important elements of the multidisciplinary approach to the management of OI. Physiotherapy helps to maintain muscle tone and optimal function. Early rather than late intervention is advocated, as immobilization after fracture reduces lean muscle mass, which leads to a decline in bone mineral density.[34,36] Psychological and social support, involvement of parents and school teachers is imperative for successful management.

Medical management, bisphosphonate therapy

Medical treatment of OI with bisphosphonates is not curative, but successfully controls symptoms. Nitrogen and non-nitrogen containing classes of bisphosphonates exist (Table III). Alendronate has a proven beneficial effect, demonstrating a decrease in fracture frequency and improved bone mineral density.[37]

Bisphosphonates are synthetic analogues of inorganic pyrophosphate that inhibit osteoclastic bone resorption. The primary effect is the inhibition of protein prenylation and guanosine triphosphatase formation, which leads to osteoclast

apoptosis.[38] Oral bisphosphonates have a very poor rate of gastrointestinal absorption.[39] Of the absorbed bisphosphonate, 20% to 80% is incorporated into the skeleton. Bisphosphonates are then slowly released into the system, with a half-life of 1.5 to 10 years. The earliest response to treatment usually occurs in 1 to 6 weeks after the initiation of therapy. Studies have shown that there is marked reduction in chronic bone pain, improvement in ambulation, decrease in incidence of fractures and improvement in bone mineral density.[40]

Biochemical markers, namely the serum concentration of calcium and phosphate are used for treatment monitoring. Serum calcium and phosphate concentrations decrease for 2 to 4 weeks, and that of alkaline phosphatase decreases for 3 to 4 months. Both oral and intravenous bisphosphonates are equally safe for children with OI. The duration of therapy should be limited to approximately two years. Therapy leads to suppression of bone metabolism for almost two years even after cessation of therapy,[41] and bone mass continues to increase after treatment stops.

Because bisphosphonates interfere with bone formation and resorption, some authors believe that it may change the course of fracture healing, and in some cases healing of osteotomies.[42-43] Thus it is advised to temporarily stop bisphosphonates during periods of fracture healing and deformity corrections. Osteonecrosis of the jaw is a rare condition which may occur with bisphosphonate therapy although its exact incidence is unknown.

Surgical management

The main aim of surgical intervention in patients with OI is to prevent and correct long-bone deformities that impair function. The spectrum of surgery ranges from minor soft tissue procedures to more complicated reconstructive procedures.[44-46] Deformities of the femur and tibia undergo reconstruction more frequently than the humerus,[46] and forearm intervention is rarely indicated.

Long bone fractures

Patients with OI may present with fractures at any age. Fractures in a new-born may be splinted with padded tongue depressors, aluminium splints, or plaster splints. Immobilisation should last for a short period, usually a week or two.

Fractures in children older than two years should be treated by means of reduction and casting, percutaneous pinning, or internal fixation. Rigid implants such as pins and plates or screws are not recommended, as stiff devices create stress risers within the bone, predisposing to pathological fractures.[47]

The classical method oflong bone fixation in OI is intramedullary rods with or without osteotomies (Figure 2). Various types of intramedullary rods are available to address issues related to surgery, bone size, and the prospect for growth.[48] Two major categories of intramedullary rods are telescopic and non-telescopic. Telescopic rods expand during growth and thus theoretically obviate revision surgery, and include Dubow–Bailey rods, Fassier–Duval rods, and Sheffield rods. Telescopic rods are associated with loosening and migration of the T-piece into the metaphysis.[49]

Non-telescopic rods do not expand and require replacement once the child's bone lengthens and begins to bow. These rods are cheap and redily available and easy to use. Non-telescopic rods may be the only option for children with very short, thin bones. The most common non-telescopic rods in use are Kirschner wires, Rush rods, Williams rods and elastic rods. In young adult patients, external fixation with an Ilizarov circular fixator and osteotomy can be used to correct long-bone deformity.[50]

Fractures and osteotomies in patients with OI usually heal well. However, non union can occur in some patients. The incidence of non-union in OI has been extensively reviewed. Gamble and associates reported 12 nonunions in 10 patients which occurred most frequently in the femur and humerus, but also in the radius, ulna, and pubis.[51]

Perioperative and surgical technique considerations

Care should be taken during intubation of a potentially fragile cervical spine and increased incidence of cranial settling.[52] Occurrence of malignant hyperthermia has been documented in the literature but the relationship appears weak.[53] Due to rigid and low elasticity of the skin and poor vascularity, the rate of infection and skin breakdown is high in patients with OI. Care should be taken whilst transferring patients to avoid fracture.

Flat, thin cortices provide a technical challenge for insertion of intramedullary rods to long bone fractures, and rod cut-out is a recognized complication. Severe deformities posees a challenge in acute correction due to risk of neurovascular compromise, and long bones may require shortening to accommodate neurovascular structures.

Future therapies

Sclerostin, an osteoblast inhibitor, has been studied in clinical trials. Antibodies to sclerostin are used for treatment for osteoporosis with a goal to increase bone density. Its antibody appeared to be effective in a mouse model of moderately severe OI.[54-55] It has been postulated that TGFb is secreted by osteoblasts which resorbs bone. Transforming growth factor activity is found to be excessive in OI. Thus anti-TGFb therapy might be beneficial for future treatment of OI.[56] Bone marrow transplant[57] or mesenchymal stem cell transplantation[58] have also been investigated for use in OI, but significant risks have been identified. Gene therapy has very promising results.[59]

Methods

The Aim: The purpose of this collective review was to analyse the diversity of orthopedic manifestations of OI through a systematic review of the literature. Search Strategy: An electronic search was performed that included Google Scholar, PubMed, and Elsevier. The search was conducted according to 'preferred reporting items for systematic reviews and meta-analyses' (PRISMA) guidelines (Figure 3). Data extraction and analysis: A computer based search was conducted and the keywords included were 'osteogenesis imperfecta' and 'orthopedic manifestations'. The period of review was from 1970 to 2013 without language restrictions. The following articles were included: randomized controlled trials; review articles; meta-analysis; and case reports which described the classification, clinical and radiological manifestations, and treatment of OI.

Results

The orthopedic manifestations of OI have been summarized in Table IV.

Spine

The pathogenesis of spinal deformities in OI is complex and is attributed to combination of weak bone and ligamentous laxity. Vertebral growth plates are prone to microfractures, resulting in growth inhibition and vertebral abnormalities. Intervertebral discs are often stronger than vertebral body bone.[60-62] The resultant compression fractures give the vertebrae a codfish appearance (Figure 4).

Spinal fractures

In patients with OI vertebral collapse, compression fractures are commonly seen, and the incidence increases with age. Norimatsu relates it to upright posture and the effect of axial loading on the weak spinal column.[63]

Craniocervical junction and cervical abnormalities

The upper cervical spine is rarely affected in OI. Though patients do not develop acute symptoms, one of the most serious abnormalities that can occur is basilar invagination. Pozo et al. reviewed three patients with basilar invagination and postulated that weak bone at the craniocervical junction and a relatively large head both contribute to the development of the condition.[64] Basilar invagination along with medial migration of the occipital condyles cause stenosis and interfere with cerebrospinal fluid dynamics. This interference causes internal hydrocephalus and subsequent compression of the cerebellum, brain stem, and upper cervical cord. Clinically this leads to various cranial nerve abnormalities, long-tract signs, and respiratory depression.

Hyperextension at the cervicothoracic junction has been described as a rare case. This deformity is postulated to be associated with a C7 vertebral body microfracture

with posterior wedging and compensatory forward bending moment in order to withstand the weight of the macrocephalic skull (Figure 5).[65]

Sagittal and coronal deformities of the spine in OI

Multiple compression fractures of the spine and reduction in vertebral height lead to increased thoracic kyphosis or a diminished lumbar lordosis. These progress to global sagittal trunk imbalance.[66] With increasing age, the spinal deformity worsens and hence the complications such as back pain, respiratory distress and nerve root compression may develop. The natural course of the spinal deformity is usually unpredictable.[62] Ivo et al. stated that bracing alone fails to control the curvature and often early spine fusion with or without instrumentation is considered to be a viable option.[67]

Spondylolysis & spondyloptosis or spondylolisthesis

Due to the bone fragility and multiple compression fractures of the vertebrae, an increased incidence of spondylolysis and spondylolisthesis is seen. Ivo et al. [67] postulated that hyperlordosis of the lumbar spine was caused by elongation of the lumbar pedicles and consecutive spondylolisthesis (Figure 6). Despite such deformities, neurological deficits do not usually occur. Absence of neurology in these patients is attributed to associated dural ectasia.

Upper and lower extremities

Lower limbs

The lower limb bones are more frequently fractured, and fracture patterns depend on injury mechanism, severity of bone fragility, and the presence of pre-existing deformity acting as a stress riser. Any fracture pattern may be seen and no particular pattern is specifically diagnostic.[68]

Fractures heal at a normal rate in OI and non-union occurs relatively rarely.[68-69] Fracture callus is typically wispy, but on rare occasions it may be large and hyperplastic (Figure 7) resembling osteogenic sarcoma on radiographs.

In the lower extremity, the femur is the most commonly fractured bone. The intertrochanteric and subtrochanteric regions are the most common sites leading to coxa vara and trochanteric overgrowth (Figure 8). [70] Multiple transverse fractures of long bones, combined with muscle contraction across the weakened diaphysis, leads to long bone bowing. Typically, anterolateral bowing of the femur and anterior or anteromedial bowing of the tibia (sabre shin deformity) may occur. Clinically the shaft of long bones is flattened mediolaterally and often rotated in addition to the curvature.

Multiple long bone deformities of the limbs are caused by angulations and overriding of healed fractures, growth disturbance at the physes, and marked kyphoscoliosis results in short stature. Pes valgus and club foot deformities are commonly seen. One case of associated developmental dysplasia of the hip has been described.[71] Adults are predisposed to rupture of the patellar ligament or Achilles tendon.[72-73]

Upper limbs

Upper limb fractures are relatively rare in comparison to those of lower limbs. Multiple transverse fractures of the humerus lead to anterolateral bowing. In patients with OI type 5, Sillence has shown that calcification of the interosseous membrane between the radius and ulna restricts forearm rotation. Angular deformity and repetitive fractures with exuberant callus formation leads to radial head dislocation (Figure 9). Angulation is generally greater in the upper part of both bones of the forearm.

Bowing and curvatures of the upper limbs are attributed to weight bearing through the upper limbs while sitting in a tripod position in bed for prolonged periods. Fractures around the elbow often develop cubitus varus or valgus with flexion

contracture.[70] A fracture that occurs commonly in mildly affected patients with Sillence type 1 disease is a displaced fracture of the olecranon.[24]

Pelvis

The characteristic appearance of the pelvis in OI is referred to as "wine glass pelvis". Due to soft bone, acetabular protrusio develops. There is usually progressive restriction of hip movements with protrusio. Wenger reported a case of protrusio which resulted in colonic obstruction.[74]

Connective tissues

Increased capillary fragility caused by the underlying collagen defect is associated with the tendency to bruise easily in OI. Evensen has postulated decreased platelet retention and reduced factor VIII in patients with OI.[75] Hansen studied the mechanical properties of the skin and found that their skin is much stiffer and less elastic than normal individuals.[76] Core muscle strength is much reduced,[77-78] and joint hyperlaxity is common, especially in affected females, which can lead to dislocation of hips and the radial heads.

Skull

One of the pathognomonic radiologic manifestations of OI occurs in the skull. The occiput becomes prominent (“Darth Vader” appearance) or a flattening of the cranial vault with transverse in folding of the cranial base (“Tam O’Shanter skull”), (Figure 10). These deformities are however very rare.[79] Patients with OI often have triangular faces.

In many instances, radiographs reveal multiple wormian bones, often ten or more,[80] that lend a “mosaic” or “paving” appearance to the cranial vault (Figure 11). Wormian bones are a subset of the small intrasutural bones that lie between the

cranial sutures formed by the bones of the skull vault. The term wormian is reserved for abnormal intrasutural bones that are typically found around the lambdoid suture.

Summary

Osteogenesis imperfecta is a group of genetic disorders with high musculoskeletal morbidity. Management of children affected with severe forms of OI may have a debilitating psychosocial impact on their family members. Though fractures heal, the deformities of long bones, soft tissue contractures and soft bones compound management strategies. A multidisciplinary approach in the management of OI is essential to achieve long term goals. Newer therapies like bisphosphonates, sclerostin, transformin growth factors and gene therapy have shown promising results.

Surgery in OI patients requires considerable pre-operative planning with regards to anaesthetic issues, bone quality and implant / bone compatibility. This review highlights the complexity of orthopedic manifestations of OI and available treatment.

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Figures and figure legends

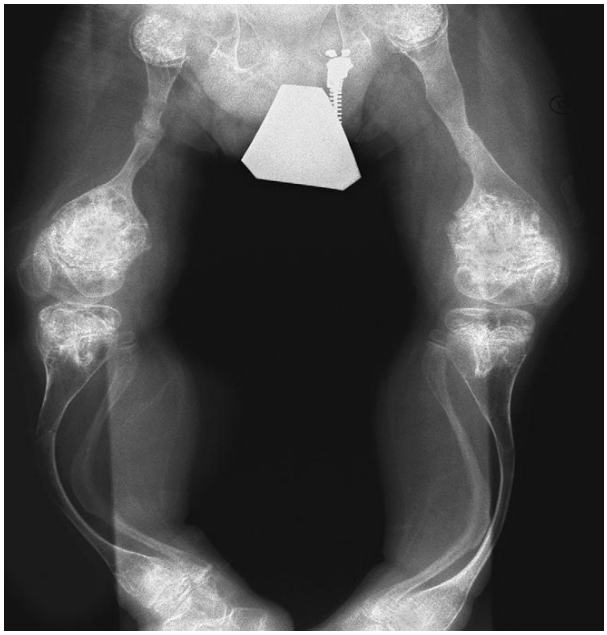


Figure 1. Bilateral lower limb radiograph shows “popcorn” appearance of the epiphyses. Severe OI causes distortion of the growth plates, with zones of partially calcified cartilage and broadening of the epiphyses.

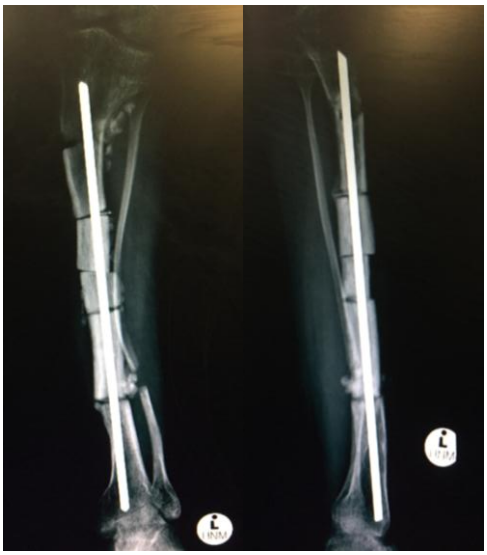
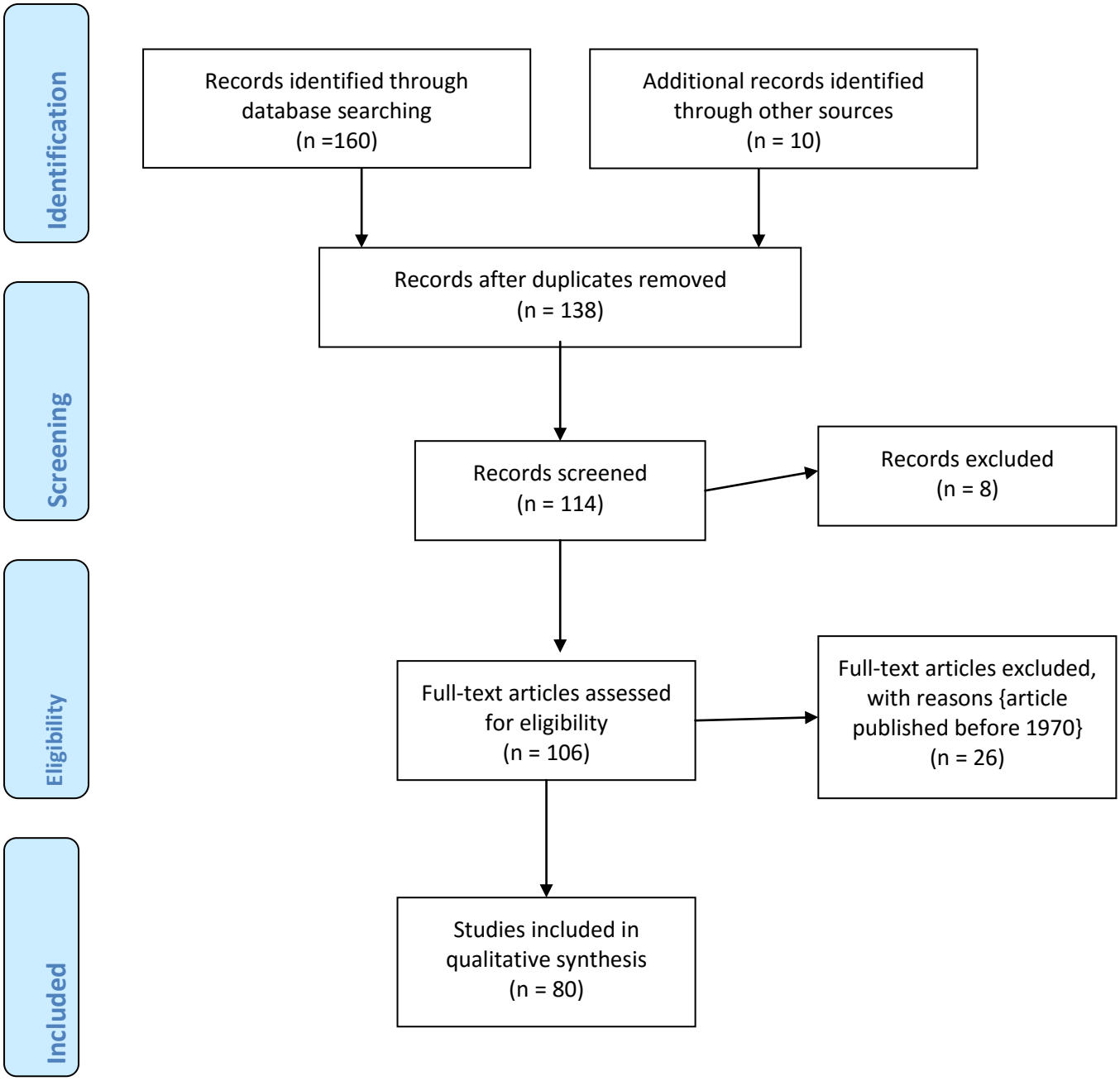


Figure 2. Anteroposterior and lateral radiographs of left tibia and fibula demonstrating segmentation of the tibia with an intramedullary rod in situ

Figure 3. PRISMA flow diagram



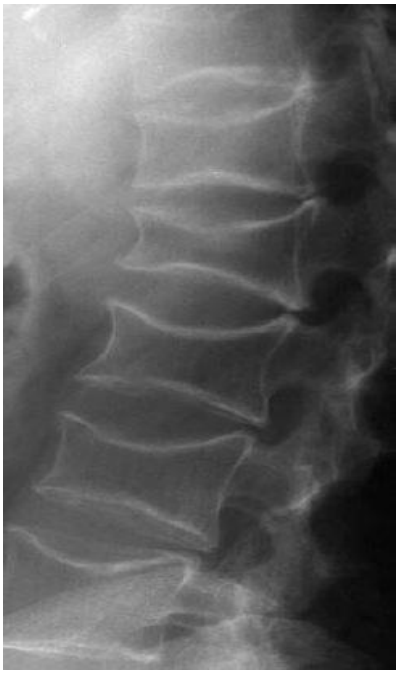


Figure 4. Lateral radiograph of thoracolumbar spine demonstrating cod fish vertebra appearance (biconcave compression fractures)

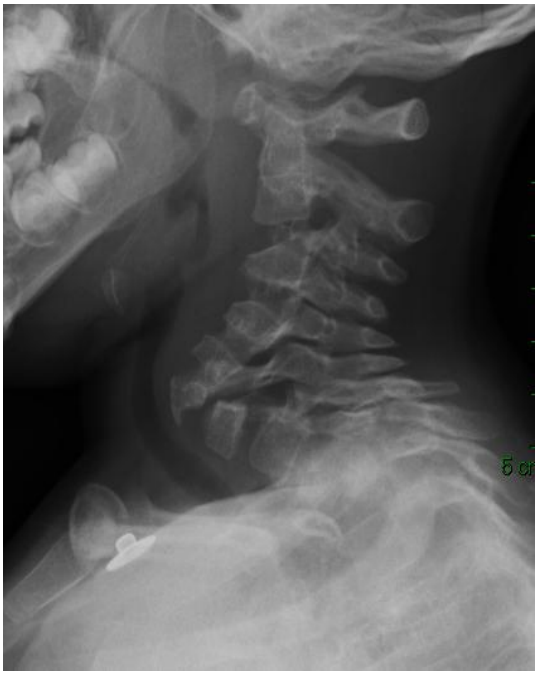


Figure 5. Lateral radiograph of the cervical spine showing the hyperextension deformity at the cervicothoracic junction

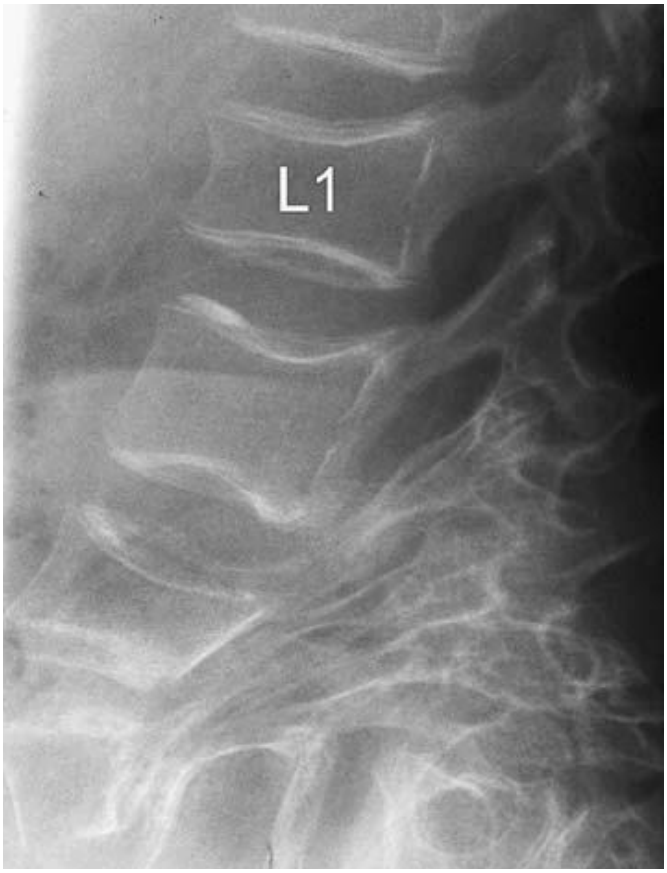


Figure 6. Lateral radiograph of upper lumbar spine, showing spondylolisthesis caused by extreme elongation of lumbar pedicles.

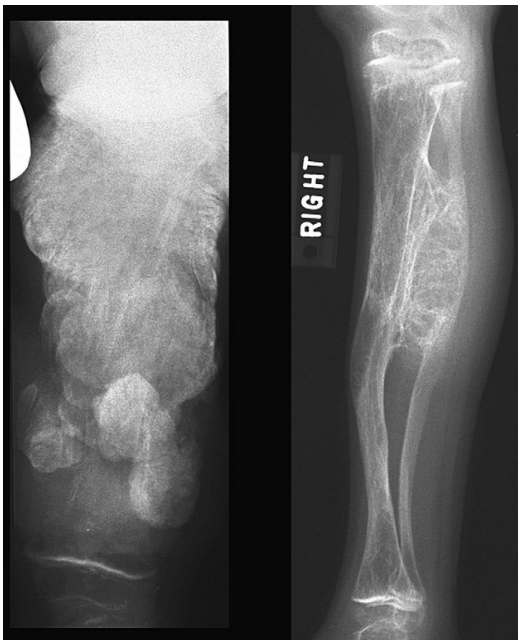


Figure 7. Hyperplastic callus resembling osteosarcoma

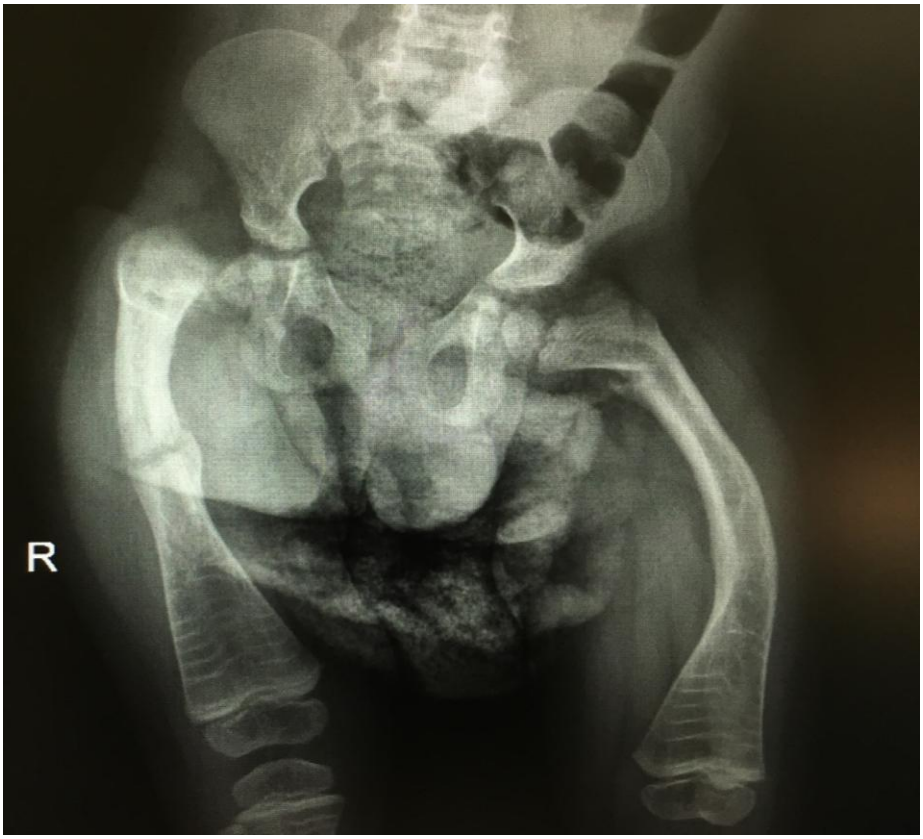


Figure 8. Anteroposterior radiograph of the pelvis and both femurs, demonstrating fractures of the right femoral neck, left femur subtrochanteric region and right femur diaphysis with subsequent coxa vara deformity, trochanteric overgrowth and anteromedial bowing of both femurs.

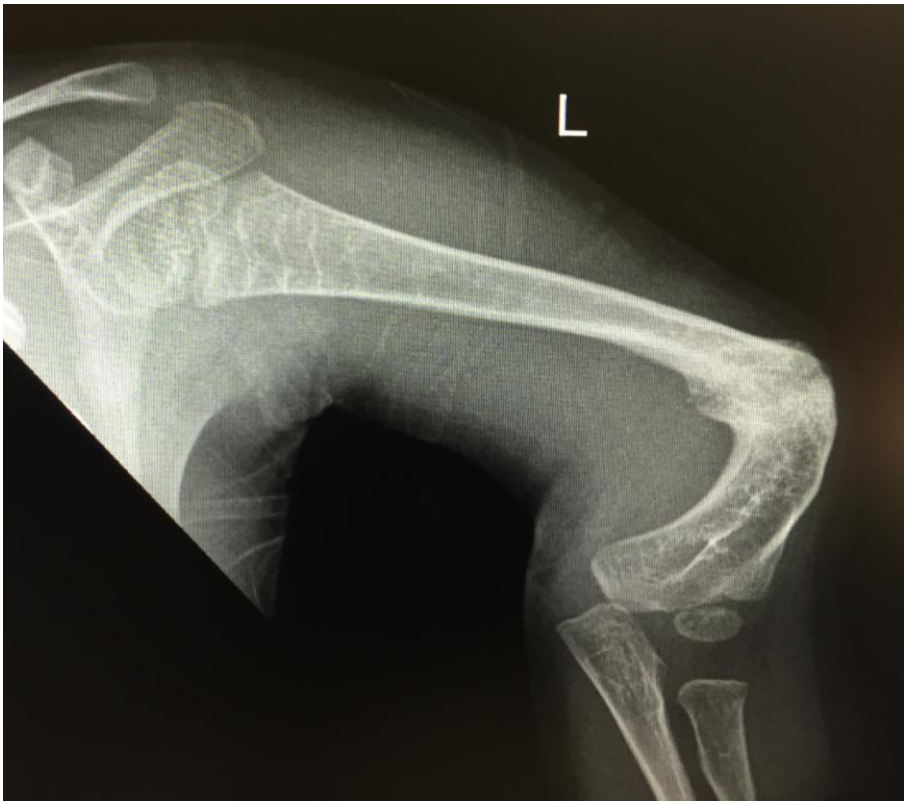


Figure 9. Malunited humerus fracture with cubitus valgus and radial head dislocation

Figure 10. Darth Vader and Tam O'Shanter images, to which skull deformities in OI have been compared

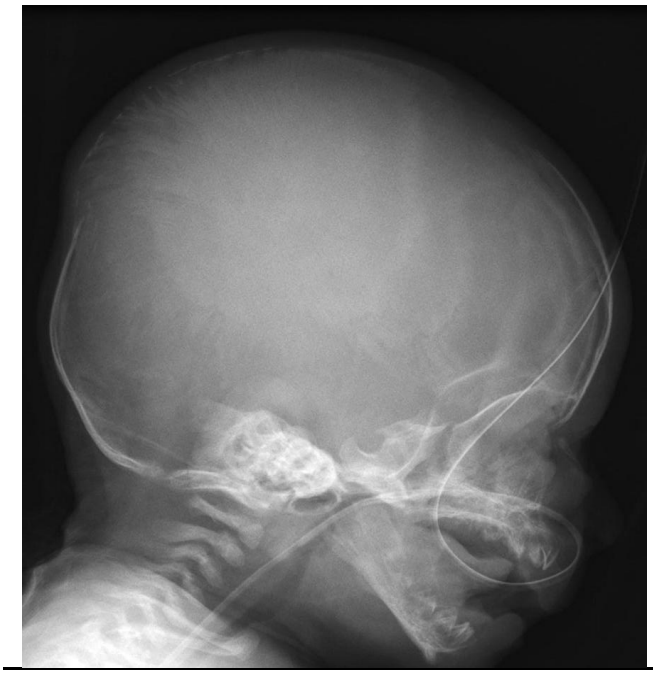


Figure 11. Lateral radiograph of skull in OI demonstrating wormian bones

Tables

Table I. Radiographic characteristics of the different types of OI

Type	Bowing of long bones	Biconcave vertebrae	Trefoil pelvis	Cystic changes	Cortex of long bones absent	Cortex of ribs absent
A	+ -	-	-	-	-	-
B	+	+	-	-	-	-
C	+	+	+	-	-	-
D	+	+	+-	+	+	-
E	+	+	+	+	+	-
F	+	+	-	-	+	+

Table II. Sillence classification expanded with OI types 5-8 as proposed by Rauch (2004) & Cabral (2007)

Sillence type	**Clinical severity**	**Mutated gene**	**Mode of inheritance**
1	Mild non-deforming	COL1A1/2	AD
2	Perinatal lethal	COL1A1/2	AD
3	Severely deforming	COL1A1/2	AD
4	Moderately deforming	COL1A1/2	AD
5	Moderately deforming	Unknown	AD
6	Moderately or severely deforming	Unknown	AR
7	Moderately deforming	CRTAP	AR
8	Severely deforming to perinatal lethal	LEPRE1	AR

Abbreviations: AD, autosomal dominant; AR, autosomal recessive.

Table III. Bisphosphonates used for OI

Drug name	Class	Generation	Administration
Etidronate	Non-nitrogen containing	1st	Oral
Clodronate	Non-nitrogen containing	1st	Oral or IV
Pamidronate	Nitrogen containing	2nd	Intravenous
Ibandronate	Nitrogen containing	2nd	Oral or IV
Alendronate	Nitrogen containing	2nd	Oral
Risedronate	Nitrogen containing	3rd	Oral
Zolendronate	Nitrogen containing	3rd	Intravenous

Table IV. Skeletal manifestations: clinical and radiographic features

Anatomical region involved	**Skeletal manifestation**
General	Short stature
Skull	Broad forehead; flattened posterior cranium; overhanging occiput; bulging calvaria (wormian bones); triangular face shape
Long bones	Anterior bowing of humerus, tibia and fibula; lateral bowing of femur, radius and ulna; dislocation of radial head; bone fragility characterized by multiple pathologic fractures resulting in bone deformity
Spine	Thoracic kyphoscoliosis; elongation of lumbar and cervical pedicles; vertebral body compression fractures; codfish appearance
Pelvis	Trefoil–shaped pelvis with protrusio acetabuli; coxa vara; wine glass appearance of pelvis
Thorax	Multiple rib fractures; moulding of the soft thorax; pectus excavatum or carinatum

Hyperextension at the cervicodorsal junction in osteogenesis imperfecta - a case report

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Abstract

Hyperextension at the cervico-dorsal (CD) junction is rare in osteogenesis imperfecta (OI) with no cases being reported in the literature. We report a three-year-old child with OI (Sillence type III[2]) who presented with: hyperextension at CD junction; low bone mass; thoracolumbar kyphosis; bilateral anterolateral bowing of femora; and failure to thrive.

Key words: hyperextension, cervico-dorsal junction, osteogenesis imperfecta

Introduction

Osteogenesis imperfecta (OI) results from mutations in genes encoding for type I collagen. Collagen is the major structural protein in bone, ligaments, tendons, skin, sclera and dentin.[1]

Type I collagen is also an integral component of several extraskeletal tissues leading to dentinogenesis imperfecta, blue sclerae, hearing impairment and hyperlaxity of the skin and ligaments.[7]

Mutant expression produces non-functional collagen (severe OI) or insufficient quantities of collagen (mild OI).[1]

The pathogenesis of spinal deformities in OI is still unknown, but is thought to be caused primarily by a combination of vertebral micro fractures due to the fragility of the bones and injury to the vertebral growth plate. Ligamentous laxity, limb-length discrepancy, pelvic obliquity, and abnormalities of the discs are secondary factors.[4-6]

In severe forms of OI, progression of multiple compression fractures of the spine and vertebral height shortening may be responsible for a global sagittal trunk imbalance.[3,4,9,17]

Studies have indicated that the incidence increases with age. This may be due to the upright posture and the effect of axial loading on the weak spinal column.[4,5,8,9] It has been found[4,6,8,10] that the intervertebral discs are stronger than the bone of the vertebral bodies and that compression fractures give the vertebrae a codfish appearance.

We describe a case of hyperextension of the CD junction.

The case report

A three-year-old child was referred with OI with hyperextension at the CD junction.

Perinatal history revealed normal vaginal delivery but delayed developmental milestones. The child was not able to lift her head until the age of three months. The child had sustained multiple long bone fractures following trivial trauma, which included bilateral femora and right humerus. The child was on regular follow-up with endocrinologists, and was treated with zoledronic acid.

On general examination the child had macrocephaly, blue sclera and poor dentition as well as kyphotic deformity of the cervical and thoracic spine. She was not able to stand or crawl, but could sit with support.

The child was spastic (Ashworth 2)[15] with altered sensory level from T2 and associated bowel and bladder involvement.

Further examination revealed bilateral anterolateral bowing of femora with associated limb length discrepancy on the left lower limb.

CT scan revealed CD junction hyperextension with elongation of the pedicles and attenuation of the posterior elements (*Figure 1*). There was no evidence of fractures.

The pathogenesis of spinal deformities in OI is thought to be caused primarily by a combination of vertebral micro fractures due to the fragility of the bones and injury to the vertebral growth plate

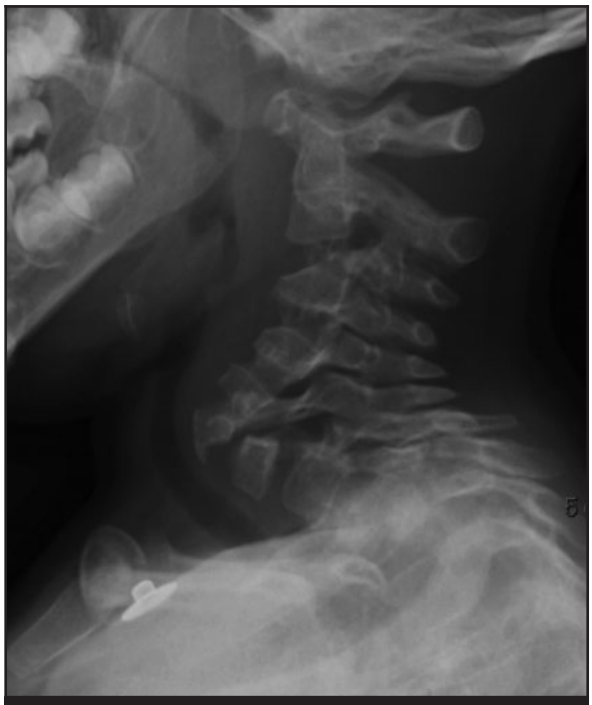

Figure 1. Sagittal X-ray of Cx spine showing the hyperextension deformity at the CD junction

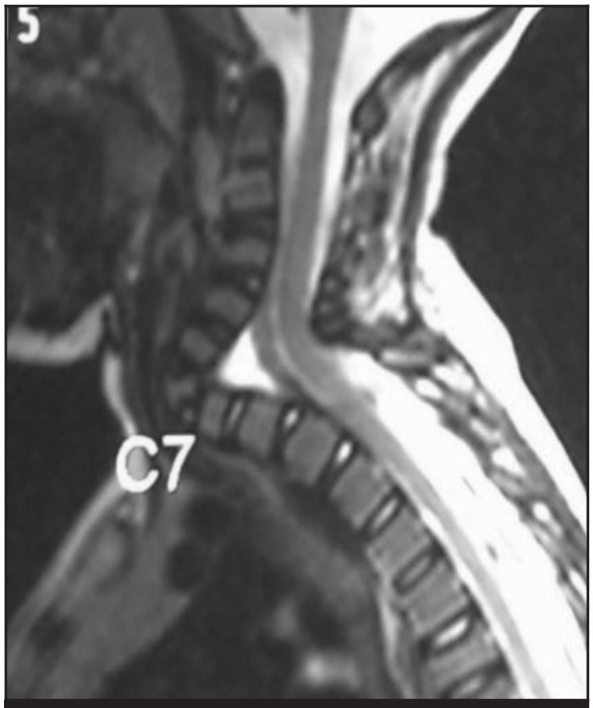

Figure 2. MRI scans showing the widening of the canal

Further images showed scalloping and wedging at the posterior vertebral body at the level of C7 with associated hyperextension.

MRI scans showed widening of the canal at the same level (*Figure* 2).

Discussion

Although OI is a well-known skeletal disease, there have been only a few reports of spondylolisthesis in the lumbar spine.[7] Familiarity with the normal developmental anatomy and radiographic features, along with knowledge of the common manifestations of hereditary and systemic diseases, are prerequisite to understanding the disorders that affect the paediatric cervical spine.[13]

The transition of the 'C'-shaped vertebral column to an 'S' shape occurs as a child starts to sit and stand with development of cervical and lumbar lordosis respectively. The C-spine essentially is free to rotate about the CD junction due to the relative immobility of the trunk during head movement. The C-spine thus acts as a cantilever beam with the 'fixed end' at the CD junction, the location of the highest stresses.

The spine depends upon a balance of forces during growth and development. Pathologies affecting the bony or soft tissue component around the spine could lead to deformity in different planes.

OI disrupts the musculoskeletal matrix resulting in change in the morphology of vertebral bodies which may result in a spinal deformity.

In our patient the hyperextension deformity might be associated with a C7 vertebral micro fracture with posterior wedging and compensatory forward bending moment in order to withstand the weight of the macro-cephalic skull. Furthermore delayed milestones with the inability to lift the head might have led to persistent kyphosis of the cervical spine in order to maintain the mechanical axis with the thoracic spine.

As shown by Basu *et al*[14] elongation of pedicles with resultant rapid progression of spondylolisthesis leads to persistent hyperlordosis of the spine above.

Pathologies around the CD junction give rise to a kyphotic deformity and are associated with neurological deficits because of the mechanical effects and smaller size of the canal and tenuous blood supply to the lower cervical cord.[11]

Ronald *et al* reported three patients with OI showing angular hyperlordosis caused by elongation of the lumbar pedicles and consecutive spondylolisthesis.[7] Our patient had elongation of the pedicles and crowding of posterior elements with associated spondylolisthesis and resultant CD junction hyperextension.

OI disrupts the musculoskeletal matrix resulting in change in the morphology of vertebral bodies which may result in a spinal deformity

During childhood with increased mechanical loads, pedicle elongation and hyperlordosis shows a rapid progression.[3] This fits the hypothesis that osteopaenia causes increased micro damage in OI bones, resulting in increased bone remodelling and, with raised mechanical strains, progressive deformations.

Basu *et al*[14] reported successful treatment of patients suffering from spondylolisthesis in OI due to lumbar pedicle elongation with interbody fusion without instrument; whereas Ronald Ivo *et al*[7] treated three patients with spondylolisthesis due to lumbar pedicle elongation with laminectomy and posterolateral fusion.

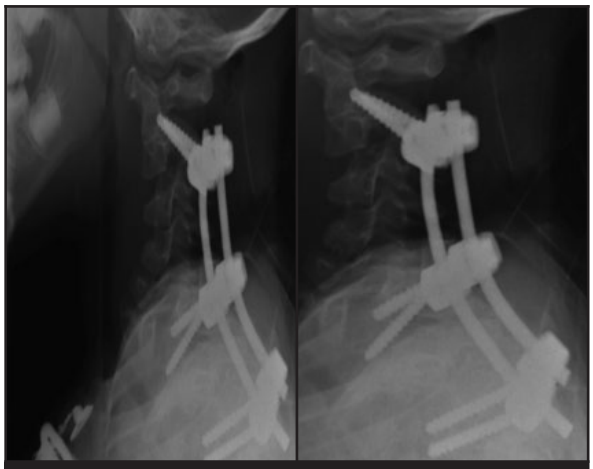

Figure 3. Post-operative lateral X-rays of Cx spine showing posterior instrumentation from C2 to T2

Our patient was treated with cervical traction for a period of six weeks followed by posterior instrumentation.

Surgery was performed in two stages. Initially the child was kept on cervical traction for a period of six weeks. Pin site care was done on a regular basis and no infection was encountered during the period.

Due to the soft and fragile bony architecture which was encountered during surgery, posterior decompression and instrumentation with pedicle screws and rods was performed (*Figure 3*).

She has now been followed up for 12 months after her surgery. At the latest follow-up her neurology has improved to Frankel D grade.[16]

Conclusion

Although there are case reports on the management of severe kyphotic deformities of the thoracolumbar spine in OI[4,6,8,12] there are no reports addressing the pathology around the CD junction with hyperextension deformity. We have presented a unique case of OI with hyperextension deformity at the CD junction.

The content of this article is the sole work of the authors. No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this article.

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MMED PROTOCOL

Collective review

Dr AD Bhatta

PG No 213571859

Title of study:

Orthopaedic manifestations of Osteogenesis Imperfecta (OI) – A collective review

Aim of the study:

This study will highlight a critical overview of the current literature with respect to 'Orthopaedic manifestations of Osteogenesis Imperfecta'. The study will focus on delineating spectrum of orthopaedic manifestations. The study will also deal with epidemiology, pathology, treatment and its complications.

Specific objectives

- Study the epidemiology of OI
- The classification system of OI
- Describe the pathology and pathogenesis of OI
- Identify the regional affectation of OI
- Establish the role of Orthopaedic surgeon in management of OI

Background

Osteogenesis Imperfecta is one of the commonest of the genetic disorders of bone; with an estimated incidence of 1 in 20,000. The condition is hereditary and is characterised by fragile bones, spinal deformity, blue sclera, deafness, laxity of joints and a tendency towards improvements with age.

OI results from mutations in genes encoding for type I collagen. The Sillence classification has been used to classify OI according to its clinical severity.

The clinical features vary considerably, according to the severity of the condition. The most striking abnormality is the propensity to fracture, generally after minor trauma and often without much pain or swelling.

In most cases the clinical and radiological features are so distinctive that the diagnosis is not in doubt. However, mistakes have been made and rare disorders causing multiple fractures may have to be excluded by laboratory tests. In hypophosphatasia, for example, the serum alkaline phosphatase level is very low.

It becomes imperative in reviewing the topic to understand the pathophysiology, clinical variants and regions of skeletal involvement in order to address the pathology.

Literature

Osteogenesis Imperfecta is a rare genetic disorder that causes increased bone fragility. OI results from mutations in genes encoding for type I collagen. Collagen is the major structural protein in bone, ligaments, tendons, skin, sclera, and dentin. [1] The main clinical characteristics is increased bone fragility, which varies widely in severity, ranging from intrauterine fractures and perinatal death to mild forms that remain asymptomatic until late in adult life.[2,3]

OI is classified into various forms depending upon on age of presentation, genetic abnormality and clinical severity. The Sillence [4] classification has been used to classify OI according to its clinical severity into four different types. Clinical severity varies widely depending on its phenotypes and currently eight types are identified. [5, 6]

Orthopedic manifestations range from angular bone deformity and curvature, recurrent fractures, ossification of interosseous membrane of the forearm, radial head dislocations, ankylosis of hips, pelvic deformity, spondylolisthesis of lumbar vertebrae and deformities of spine altering the sagittal balance of the spine.

Treatment of OI depends on the severity of the disease and on the age of the patient; in any case a treatment strategy should provide the maximum of long term function and autonomy.[7, 8, 9]

Lifelong multidisciplinary management is imperative in order to address different aspects of the disease. Intravenous bisphosphonate therapy in childhood is the most extensively studied treatment

and has been proved beneficial. [10] Prevention of vitamin D and calcium deficiency is essential throughout life. Various orthopedic and surgical techniques are available for reducing fractures and correcting the deformities. Pain is common and should be addressed effectively.

Key References

1. Cole WG. Advances in Osteogenesis Imperfecta. Clin Orthop 2002; 401:6-16.
2. Folino A et Al. New perspectives on Osteogenesis Imperfecta. Nat Rev Endocrinol 2011; 7:540-557
3. Munns et Al. Delayed osteotomy but not fracture healing in pediatric Osteogenesis Imperfecta patients receiving pamidronate. J Bone Miner Res 2004;19:1779-1786
4. Sillence DO et AL. Genetic heterogeneity in Osteogenesis Imperfecta. J Med Genet 1979; 16:101-16
5. Marini JC et Al. Null mutations in LEPRE 1 and CRTAP cause severe recessive Osteogenesis Imperfecta. Cell Tissue Res 2010;339(1):50-70
6. Rauch F et AL. Relationship between genotype and skeletal phenotype in children and adolescents with Osteogenesis Imperfecta. J Bone Miner Res 2009;9999(99A):1-30
7. Antoniazzi F et Al. Osteogenesis Imperfecta: practical treatment guidelines. *Paediatr Drugs*. 2000; 2:465–488.
8. Rauch F, Glorieux FH. Osteogenesis Imperfecta, current and future medical treatment. *Am J Med Genet C Semin Med Genet*. 2005; 139C:31–37.
9. Glorieux FH. Treatment of Osteogenesis Imperfecta: who, why, what? *Horm Res*. 2007; 68:8–11
10. Glorieux F et AL. Cyclic administration of pamidronate in children with severe Osteogenesis Imperfecta. N Engl J M 339 (1998). Pp.947-952

Research design

Search strategy:

A collective review of the literature via the relevant search engines and search terms will be undertaken.

Search engines and electronic databases:

- UKZN Primo search
- Biomed central
- PubMed
- Science direct
- Cochrane Library
- EBSCO host
- Google scholar

AN experienced medical librarian will be consulted to improve the general approaches for conducting a comprehensive search of the above databases.

Relevant search terms will include the following keywords:

- Osteogenesis
- Imperfecta
- Orthopaedic manifestations
- Deformities
- Silience
- Brittle bone

The inclusion criteria:

- Human subjects.
- No age predilection
- English language text
- Period – year 1970 to the present

- Studies from both developed and developing countries

Data collection methods:

Academic books, journals and various publications on the subject will be used to collect the relevant data. Information will be gathered from studies that include randomized controlled trials, review articles, case reports and systemic reviews.

Literature published from late 70's will be used for this review since most of the initial works were done around that period.

Studies meeting the obvious inclusion criteria will be assessed for its inclusion. Microsoft word, excel will be used to summarise and categorise the main results.

Data analysis:

Studies will be evaluated through content analysis, as meta-analyses will not be feasible due to the vast variety of study designs and variables.

The study will focus only on qualitative research design.

The study will be analysed by comparing and contrasting content related to

- Epidemiology
- Pathology
- Clinical manifestations
- Management / treatment strategies
- Complications
- Outcome measurements

The data will be categorised and crossed checked against the inclusion and exclusion criteria. The findings will be evaluated and conclusions will be drawn. Clinical significance with regards to Orthopaedic manifestation of OI will be highlighted.

Study location

University of Kwazulu Natal.

Medical school Campus

Department of Orthopaedics.

Study period

January 2014 - December 2014

Limitations to the study

The study will rely solely on databases, electronic sources for the literature search, conference proceedings as well as literature prior to the study period mentioned and the absence of two or more reviewers to independently collate and appraise the data.

Ethical considerations

This is not applicable as the study is a review of the literature and does not involve the participation of the patients, use of pharmaceutical products or any other treatment strategies.

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24 January 2014

Dr A Bhatta (Student No. 213571859)
PO Box 50342
Musgrave Road
Berea
4062

Dear Dr Bhatta

Study Title: "Orthopedic manifestations of osteogenesis Imperfecta" REF No.: EXM09/13.

I refer to your application to BREC received on 18 December 2013 and wish to advise that exemption is granted for this study because all data is already in the public domain.

This exemption will be noted at the next Biomedical Research Ethics Committee meeting to be held on **11 February 2014.**

Yours sincerely

Ms A Marimuthu
Senior Administrator: Biomedical Research Ethics Committee

cc: Dr MN Rasool

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INYUVESI
YAKWAZULU-NATALI

6 December 2013

Dr MN Rasool
Department of Orthopaedic Surgery
School of Clinical Medicine
College of Health Science

Dear Dr Rasool

MMed: **"Orthopaedic manifestations of Osteogenesis Imperfecta (OI) – A collective review.** Student: Dr A Bhatta student number: 213571859 (Department of Orthopaedic Surgery)

I am pleased to inform you that the abovementioned study has been approved.

Please note:

- The Academic Leader: Research must review any changes made to this study
- The study may not begin without approval of the Research Ethics Committee

May I take this opportunity to wish the student every success with the study.

Yours sincerely

for Dr VS Singaram
Academic Leader Research (Acting)
School of Clinical Medicine

C. Dr A Bhatta

Biomedical Research Ethics Committee
Westville Campus