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Case Report

Type III Osteogenesis Imperfecta with Severe Limb Deformities: A Report with Review of The Literature

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ABSTRACT

Background: Type III osteogenesis imperfecta (OI) is very rare. In this article, we describe the clinical features and management of a case of type III osteogenesis imperfecta with a review of the literature.
Case Report: A 5 – year - old girl presented with deformities of the bilateral lower and upper limbs. Posterior bowing of both humerus, cubitus varus deformity of both elbows, shepherd crook deformities of the femur, and anterolateral bowing of both legs were observed. She was unable to walk. Her face was triangular, and she had a kyphoscoliotic deformity of the spine. Radiographs showed osteopenia and multiple fractures at different stages of healing. The clinical and radiological findings were consistent with those of type III OI. She was treated by deformity correction of the right femur and tibia using the Sofield technique.
Discussion: OI is a disorder caused by a mutation in type 1 collagen. It is characterized by increased bone fragility, dentigerous imperfecta, and generalized ligamentous laxity. There are 18 types of OI. We describe a case of type 3 OI in which the child developed deformity of the spine and limb at a later age without involvement of the sclera. Lower limb deformities were corrected using the Sofield technique of multiple osteotomies and intramedullary nailing. The implants were removed once the osteotomies were united. After implant removal, antero-lateral bowing of the tibiae recurred.
Conclusions: Long bone deformities can be managed using the Sofield technique. Long-term follow-up is essential for the early detection and correction of recurrence

Keywords: Osteogenesis imperfecta; Osteogenesis imperfecta type 3; Sofield technique; Human and illness

INTRODUCTION

Osteogenesis imperfecta (OI) is characterized by a triad of increased bone fragility, dentigerous imperfecta, and generalized ligamentous laxity. The incidence is 0.5-1/10,000 live births. Olof Jakob Ekman (1788) did the earliest studies about OI. The basic pathophysiology of OI is a mutation in the gene coding for type 1 collagen. Approximately 18 types of OI have been described in the literature. Many of these are very rare. Based on the severity of the disease, it can be divided into non-deforming, progressively deforming, and perinatal lethal varieties. Heterogenicity of phenotypic variance can be seen with a similar type of mutation. It is ascribed to the interaction between genetic loci and environmental factors.[1] Blue sclera is common in the nondeforming type, but it is absent in progressively deforming and perinatal lethal types.[2]

Type III osteogenesis imperfecta is rare. This variety is the severe form of OI in surviving patients and can present with multiple fractures

and deformities in the fetal and perinatal period. Suspected cases can be diagnosed by routine antenatal ultrasound scanning at 14–18 weeks of gestation. Most cases of Type III OI are characterized by normal infancy followed by gradually progressive limb deformities. Type III OI can cause severe deformities that are difficult to treat. Deformity recurrence is common after treatment. In this article, we describe our experience with a case of type III OI, its clinical features, management, and a review of the literature.

CASE REPORT

A 5-year-old girl was brought to our hospital in July 2019. She was the second child of a non-consanguineous marriage. The parents noticed progressive deformity of both the upper and lower limbs for the last two years. She was born via normal vaginal delivery. The antenatal, perinatal, and postnatal periods were uneventful. The patient's developmental milestones were within normal limits. She had sustained multiple fractures following minor injuries since the age of 3 years. Gradual bowing of the upper and lower limbs was observed. Later, she developed difficulty in walking, squatting, and sitting cross-legged. There was no history of similar illnesses in her family. Her siblings were also unaffected.

At the time of presentation, she was active and playful. She was unable to walk independently. She was short-statured. The head was larger than the body. The shape of the face was triangular. No scleral discoloration was observed. Muscular hypotonia and generalised ligamentous laxity were present. She had no visual or hearing problems after ophthalmology and otolaryngology assessments.

There were dental caries with malocclusions and unerupted teeth (Figure 1A). Scoliosis of the dorsal

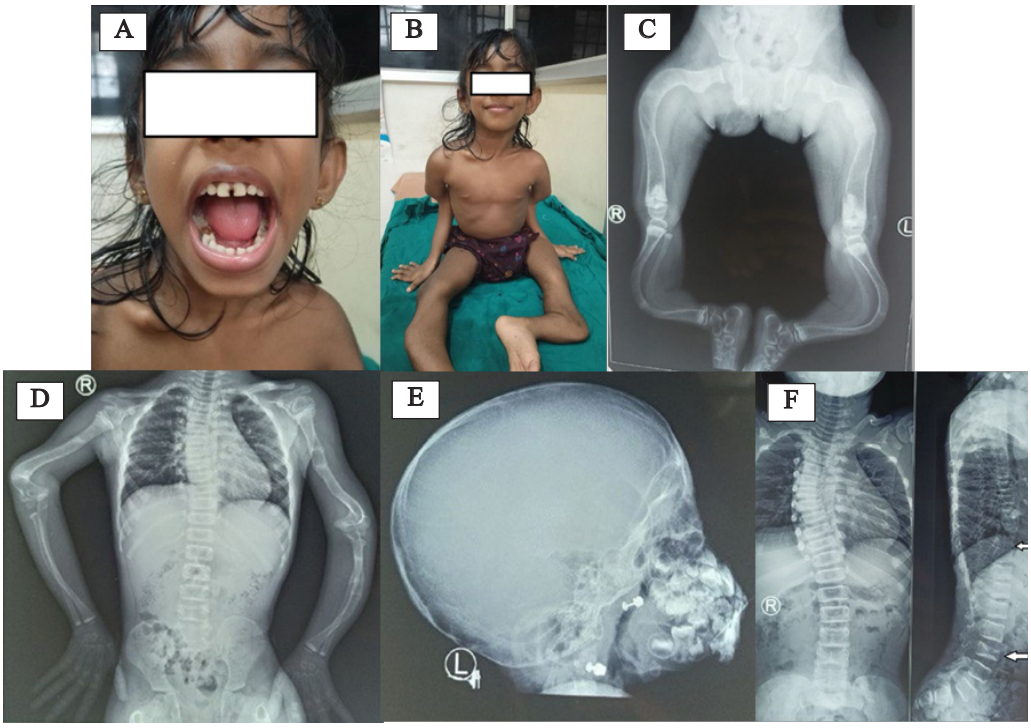

Figure 1. (A) Photograph of the oral cavity showing dental caries, broken teeth, and abnormal dentition. (B) A clinical photograph of the child showing triangular facies, a broad forehead, pectus carinatum, posterolateral bowing of the arm, lateral bowing of the bilateral thighs, and anterolateral bowing of both legs. (C) Radiograph of the lower limbs showing osteopenia with shepherd crook deformity of both femurs and anterolateral bowing of both bones of the legs. (D) The radiograph shows bilateral posterolateral bowing deformity of the lower-third humerus and anterolateral bowed forearms. (E) Lateral radiograph of the skull showing unerupted teeth, short root teeth, and dental caries. (F) The anteroposterior and lateral radiographs show scoliosis of the dorsal spine, deformities of the ribs, and compression fractures at multiple levels (arrows)

spine and pectus carinatum deformity of the chest were also observed. Posterolateral bowing of the arm and anterolateral bowing of the forearm, as well as cubitus varus deformity of both elbows, were observed. Both thighs were bowed outward with anterolateral bowing of the legs (Figure 1B).

Her haemogram was normal. Serum calcium was 8.8 mg/dl and phosphorous was 4.2 mg/dl. The serum alkaline phosphatase level was 427IU/L probably due to growth and fractures. Renal and liver function tests were also normal. The X-rays showed generalized osteopenia with multiple fractures in different bones at different stages of healing. There was severe varus deformity of the femur – shepherd crook deformity on both sides. There was anterior and lateral bowing of both bones of the leg (Figure 1C) and posterolateral bowing of the humerus and curved forearm bones (Figure 1D). Pectus carinatum with rib deformities was present. The skull X-ray showed Wormian bones and delayed eruption of teeth with dental caries (Figure 1E). There was scoliosis of the dorsal spine with compression fractures in many vertebrae (Figure 1F).

She was treated with deformity correction by Sofield Millar Kebab osteotomy of her right femur and right tibia (Figure 2A). The procedure was performed under general anesthesia. Preoperative 750 mg of cefuroxime was administered intravenously 30 minutes before the procedure. Antibiotics were continued twice daily for three days postoperatively. The child was placed in a lateral decubitus position with the operated side up. We opened the femur at the site of maximum deformity and performed osteotomy. A square nail was introduced in a retrograde manner. Another osteotomy was performed at the site where the nail hit the cortex; the procedure was repeated many times. Finally, the osteotomies were reduced to achieve maximum neutral alignment. The nail was then advanced in an antegrade fashion to fix the osteotomy and the wound was closed in layers. A similar procedure

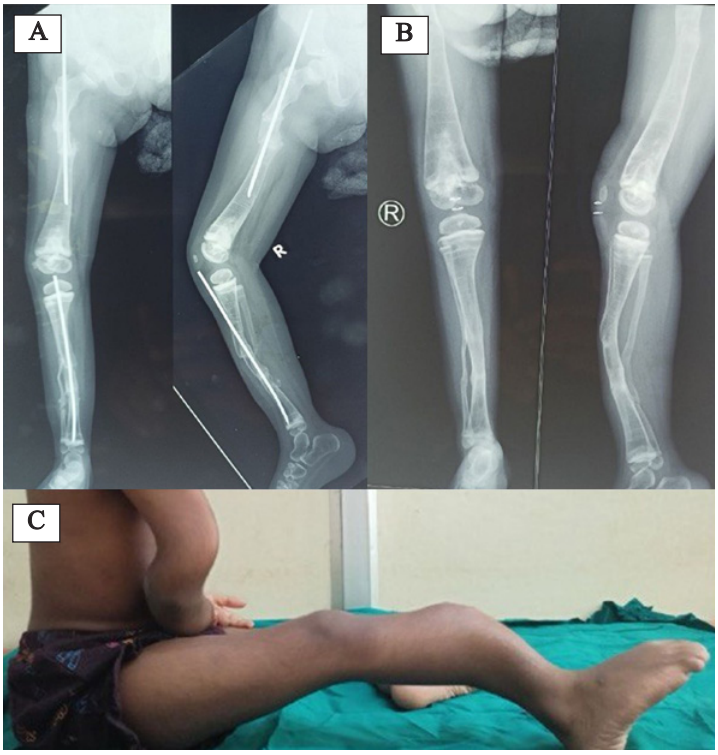

Figure 2. (A) An anteroposterior and lateral radiograph of the right lower limb showing united osteotomy with a square nail in situ in the femur and tibia. (B) The latest radiograph of the right lower limb after implant removal shows united osteotomy and recurrence of anterior bowing of the tibia. (C) The latest photograph shows a clinical picture of the right lower limb after recurrence of tibial bowing

was performed on the tibia. Postoperatively, the limb was immobilized in a long leg slab for six weeks (Figure 2B).

The procedure was performed in July 2019. After about seven months, we lost follow-up of the child due to the COVID-19 pandemic. Later, she came for a follow-up during February 2022 due to pain and irritation at her buttock due to protruding nails. An X-ray showed a union of the osteotomy site, hence we decided to remove the implants. Implant removal was performed, and the patient had near-normal alignment of both lower limbs. At the final follow-up in April, she had developed a recurrence of the deformity of both tibiae, more on the right side than on the left (Figure 2C). She is taking regular oral supplements of calcium and Vitamin D. She was on parenteral zoledronic acid once every six months.

Informed consent was obtained from the parents for the procedure and its publication. This report was written according to the CARE guidelines.

DISCUSSION

Osteogenesis imperfecta is a heterogeneous group of inherited disorders caused by defects in the extracellular matrix. It is also known as brittle bone disease. In 1840, William Vorlik coined the term osteogenesis imperfecta. OI is a generalised disorder of the connective tissue having extraosseous manifestations.[2]

The most common cause of OI is the mutation of two genes encoding type 1 collagen.[3] The most common gene mutations in OI occur in the two genes encoding type 1 collagen COL1AI and COL1A2. This mutation can occur in de novo or can be inherited from the parents. The first mutation is a quantitative mutation that produces reduced quantities of type 1 collagen. In the second type, there is a structural defect in type 1 collagen. Along with this, gene mutations that modulate osteoblast differentiation or bone mineralisation cause about 10% of moderate to severe OI.[4]

Sillence et al. proposed a classification for OI based on clinical and radiological features. Type 1 is nondeforming with blue sclera, type II perinatally lethal OI, type III progressively deforming variety, and type IV moderate to severe osteogenesis imperfect. Type 1 is the least lethal and type II is the most lethal variety. Later, many types were added according to their genotypic characteristics. Currently, there are approximately 18 types of OI (I-XVIII) (Table 1). The autosomal dominantly inherited types (I and IV) were the most common (85%). Type V is inherited in a recessive manner and is due to an interferon- mediated transmembrane 5 mutation. Type V to XVIII constitute the rest of the cases (15%).[5,6]

There was decreased cortical thickness in the OI group. Compared to normal bones, the vascular porosity of cortical bone is increased in OI. Increased Haversian canal connectivity and diameter were observed. Osteocyte lacunar porosity is also increased. The lacunae were more spherical. The cancellous bone showed fewer and thinner trabeculae. There was increased trabecular spacing and greater trabecular inhomogeneity. There was a lower bone mineral density. There is also a greater chance of vitamin D deficiency in patients with OI. All these matrix changes lead to increased bone fragility in OI.[6]

The diagnosis of OI is mainly based on clinical features and family history. The majority of patients suffer fractures in early childhood. It can occur during the intrauterine or perinatal period, childhood, or later in life. Fractures can occur with minor trauma. Short stature, bowing of the long bones, and growth deficiency can be observed. Characteristic facial features include macrocephaly, flat midface, and triangular faces. There are associated dentigerous imperfections and blue sclera in some cases. Pectus excavatum, pectus carinatum, and barrel-shaped chest deformities were observed. Scoliosis or kyphosis is observed in some cases. Apart from the blue

sclera, hearing loss, pulmonary hypoplasia, and regurgitation of cardiac valves can be seen in certain types of OI. Craniovertebral anomalies such as platybasia and basilar invagination can be present. In certain forms, restriction of forearm rotations and joint movements or craniosynostosis is present. People with OI are at higher risk of death from respiratory or gastrointestinal disease, or trauma.[3,4,7] There is decreased muscle mass and increased fatigue in patients with OI.[8,9]

The radiograph shows a generalized reduction in bone density with thinning of the cortex. The skull shows Wormian bones, dentigerous imperfecta with delayed eruption, and an increased number of caries teeth. The radiograph shows short roots of the teeth with constriction of the coronaradicular junctions. Kyphoscoliosis of the spine, platyspondyly, compression fractures with codfish vertebrae, and craniovertebral anomalies can be observed on spine X-ray. Multiple fractures, deformed long bones like shepherd crook deformity of the femur and protrucio acetabuli are seen.[10] The assessment of bone density using a DEXA scan and trabecular bone score is another method used for detecting OI. High- resolution peripheral quantitative computerized tomography (HR-pQCT) can demonstrate the lower trabecular BMD and trabecular bone microstructure alteration in patients with OI.[11]

Screening for OI can be performed when a family history is present. Perinatal lethal forms of OI can be detected in antenatal ultrasound scans by 14–16 weeks of gestation. The longitudinal growth of the fetus falls below the fifth percentile by the 18th week. Sequencing of chorionic villus samples can be used to prenatally confirm OI when a family history of disease is present. Identification of fetuses with severe limb shortening and fractures may provide information for early termination of pregnancy after genetic confirmation. The use of donor eggs or sperm is a way to avoid transmission of parental OI.[12]

Currently, there is no curative treatment for OI. Nutrition and activity are the mainstays of medical treatment. Serum calcium and vitamin D levels were checked regularly. Therefore, adequate amounts of these substances must be supplemented to maintain bone health. Bisphosphonates are frequently used in the treatment of OI. They can reduce the frequency of fractures, improve the size and shape of the vertebra, and improve bone density. A single vertebral fracture or three or more long bone fractures per year for over two years are indications for starting or resuming bisphosphonates. Anabolic drugs, such as teriparatide and inhibitors of sclerostin, have also been tested. There is much acceptance for treatment with denosumab and cell therapy.[13]

Rehabilitation plays an important role in the management of OI, but it must be individualized to improve functions. In neonates with OI, parents must be taught about positioning, handling, and transportation safety. The role of frequent head turns, prone positioning, and play in encouraging cognitive development is essential. The goal of school-going children is to meet developmental milestones as closely as possible to other children. Such social development is also important. Maximizing mobility in adolescents and young adults is important even with ambulatory aids. Braces can be used to prevent and treat deformities. Braces can also be used for treating fractures.[13,14]

Surgical treatment of fractures and deformities is challenging in OI. Surgery is often required to treat fractures and deformities. There is an increased risk of fractures during cuff inflation during monitoring of blood pressure or intravenous cannulation. The large head, large tongue, and short neck make intubation difficult. Chest deformities can cause decreased pulmonary function. Succinylcholine needs to be avoided, as there is a risk of fractures due to fasciculations. Hyperthermia and coagulation disorders are also reported in OI.[15]

There is no specific surgical technique for the treatment of type III OI. The principles and methods of surgery are similar for all types. There was no significant difference between the outcomes of surgical and conservative treatment.

The goal of fracture treatment is to maintain alignment and stability and prevent recurrence. The Sofield technique is widely used for multiple osteotomies with intramedullary fixation. Telescopic nails such as the Bailey-Dubow, Sheffield, and Fraisier-Duval rods are used. A high rate of reoperation, nail migration, malunion, and nonunion has been reported with nails. Supplementing nails with additional plates and screws was attempted to prevent this. External fixators were also used. Therefore, plate fixation alone is not recommended. Patients with Type III OI have poorer radiological outcomes after surgery. Patients with spinal deformities that are progressive after skeletal maturity or > 50 °after peak height velocity need surgical correction. Children with spinal deformities should be followed-up regularly. Posterior instrumentation is sufficient, but there is a high rate of failure due to severe osteopenia. Preoperative traction may be required for rigid deformities. The fusion must be extended to T3 or T2 proximally. Basilar invagination with headache, cranial nerve palsies, dysphagia, or myelopathy requires surgical treatment. Craniocervical fusion is commonly performed. The incidence of spondylolisthesis or spondylolysis at the L5 level is higher in children with OI. There are no clear guidelines for its management.[16]

Type III OI is associated with fractures of the long bones with malunion and severe deformities. Sometimes, in severe cases, it can be detected as early as 14 to 18 weeks of gestation by antenatal ultrasound scanning. There are no diagnostic criteria for type III OI. Multiple fractures in preschool-going children. Deformities of the trunk-like pectus carinatum and scoliosis, triangular faces, broad forehead, flat occiput, and dentigerous imperfecta are also common. There can be hypermobile joints, malaligned joints, or an increased chance of dislocations in type III OI. They have greyish-white sclera and grey- or yellow-colored teeth with enamel hypoplasia. The skin is very thin, with an increased risk of keloid formation. Increased connective tissue metabolism can lead to heat intolerance, excessive sweating, accelerated breathing, and heartbeat in some cases.[17] There was found a relatively higher incidence of autosomal recessively inherited type III OI in southern Africa, where a deleterious FKBP10 mutation was detected in those patients.[18] There is a higher failure rate for plates when used for fixation of fractures in type III OI.[19] Increased nuchal translucency and short femur can be an early sign for the diagnosis of type III OI in early gestation.[20] Zoledronic acid is a safe and effective bisphosphonate for treating type III OI.[21] There is a decreased incidence of compression fractures and upper limb fractures in children taking palmidronate in type III and IV OI.[22]

Our patient had type III osteogenesis imperfecta. She had progressive deformities of the limbs, with typical features of the face and spine. The sclera was not blue. We treated her left lower limb using the Sofield multiple osteotomy method and fixation with an intramedullary nail. However, there was a recurrence of the deformity of the tibia after implant removal. We used a single square nail for fixation, and the medullary cavity was very wide, which could be the reason for proximal migration of the nail and early removal of the implant. Telescopic nails were not available in our institution. We believe that using multiple nails to fill the medullary cavity or a plate nail construct could prevent this complication. In our opinion, the pull by the triceps suri muscle may have been responsible for the early recurrence of the anterior bowing in our case.

Type III OI is rare, and this report is based on a single case. Definitive conclusions can be derived from multicenter studies involving a larger number of participants. We present this report to highlight the rarity of type III OI. Follow-up after corrective surgery is important to detect any recurrence and initiate treatment at the earliest.

CONCLUSION

Based on our experience in treating this case, we think that surgery is essential for treating deformities in type III OI. Multiple osteotomies and intramedullary nails are good for correcting long bone deformities in OI. Telescopic nails are better for preventing complications such as proximal migration. The use of multiple nails or nail plate constructs can prevent this complication. The use of a single nail for fixation should be avoided. Long-term follow-up is essential for the early detection and correction of recurrence.

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CONFLICT OF INTEREST

The authors declare no conflict of interest

ETHICS APPROVAL

This case report was approved by the Institutional Ethics Committee. Informed consent for publication was obtained from the parents.

DATA AVAILABILITY STATEMENT

The data presented in this study are available within the article

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