JPPIPA 10(11) (2024)

Jurnal Penelitian Pendidikan IPA

Journal of Research in Science Education

http://jppipa.unram.ac.id/index.php/jppipa/index

Osteogenesis Imperfecta: Case Report and Literature Review

I Gede Bramantya Surya Mahendra[1*], Dyah Purnaning[2]

[1] Faculty of Medicine, University of Mataram, Mataram, Indonesia.
[2] Department of Orthopaedics and Traumatology, Regional General Hospital of West Nusa Tenggara Province, Mataram, Indonesia.

Received: May 19, 2024
Revised: October 04, 2024
Accepted: November 25, 2024
Published: November 30, 2024

Corresponding Author:
I Gede Bramantya Surya Mahendra
gedebramantya82@gmail.com

DOI: 10.29303/jppipa.v10i11.9342

Abstract: Osteogenesis imperfecta or brittle bone disease is a disorder of congenital bone fragility caused by genetic mutations in the procollagen type 1 code (COL1A1 and COL1A2). The global prevalence of children born with osteogenesis imperfecta is estimated to be 1 in 100,000 children worldwide. The diagnosis of osteogenesis imperfecta is based on history taking, physical examination, and supporting examination. Management of patients with osteogenesis imperfecta requires multidisciplinary treatment. There are several treatments that can be done, including conservative management, surgical management, and medical rehabilitation. This case report will discuss an 8-year-old girl who was treated at the West Nusa Tenggara Provincial Hospital with a diagnosis of closed fracture of the sinistra femur, osteogenesis imperfecta, and Congenital Talipes Equinovarus (CTEV).

Keywords: Case report; Congenital; Osteogenesis imperfecta; Pediatric

Introduction

Congenital abnormality is a condition of congenital abnormality in the musculoskeletal system that is inherited or passed down. Genetic abnormalities will pathogenetically cause many diseases. One type of congenital abnormality is osteogenesis imperfecta (Noor, 2020). Osteogenesis imperfecta is a disorder in the formation of collagen tissue that has a function as connective tissue due to gene mutations (Claeys et al., 2021; Etich et al., 2020), resulting in abnormalities in the formation of type I collagen (Wishbone-Day, 2016). The global prevalence of osteogenesis imperfecta is estimated to be 1 in 100,000 children worldwide born with osteogenesis imperfecta (Verdonk et al., 2024). In the United States, there are approximately 500,000 patients. The prevalence of osteogenesis imperfecta in Indonesia is still unknown. According to the Endocrinology Division, Department of Pediatrics, Cipto Mangunkusumo Hospital (RSCM), 70 patients suffered from osteogenesis imperfecta in the last 5 years (Pulungan et al., 2019). Cases of osteogenesis imperfecta are genetically inherited and predispose patients to multiple fractures from mild to moderate trauma, low bone mass, and bone fragility (Syafira, 2019). Based on these problems, an article was prepared that will discuss osteogenesis imperfecta with case examples.

Osteogenesis Imperfecta (OI) is a rare genetic disorder that causes bones to become brittle and prone to fractures (Lim et al., 2017; Morello, 2018). This condition is caused by mutations in the COL1A1 or COL1A2 genes, which code for type I collagen, a major component of bone tissue responsible for maintaining bone strength and elasticity (Whyte, 2017). Globally, the prevalence of OI is estimated to range from 1 in 15,000 to 1 in 20,000 live births, making it one of the rarest genetic disorders (Forlino & Marini, 2016; Shih et al., 2024).

OI consists of several types that vary in severity, ranging from type I, the mildest form, to type II, the most severe form, which often results in fatality in infancy. The primary symptom of OI is bone fragility, but other clinical signs include bone deformities, hearing loss, blue-tinted sclera, and dental issues such as dentinogenesis imperfecta (Rauch & Glorieux, 2004). The impact of OI is not only physical but also psychological, as patients often face social and emotional challenges due to physical limitations and

How to Cite:
Mahendra, I. G. B. S., & Purnaning, D. (2024). Osteogenesis Imperfecta: Case Report and Literature Review. *Jurnal Penelitian Pendidikan IPA*, *10*(11), 9106–9113. https://doi.org/10.29303/jppipa.v10i11.9342

societal stigma (Trejo & Rauch, 2016; Marini & Cabral, 2018).

Although bisphosphonate therapy has shown effectiveness in improving bone density in OI patients, it does not completely address the underlying bone fragility of the condition (Ghandforoushan et al., 2023; Liu et al., 2020). The management of OI requires a multidisciplinary approach, involving various fields such as orthopedics, physiotherapy, and psychological support to help improve patients' quality of life (Forlino & Marini, 2016).

In Indonesia, awareness and attention toward OI remain very limited. Many patients receive delayed diagnosis and treatment due to a lack of understanding about the disease, as well as the scarcity of medical facilities equipped to manage rare genetic disorders. Therefore, further research on OI is crucial to raising public awareness, improving early diagnosis, and designing better interventions for OI patients in Indonesia.

This research is expected to contribute to enhancing the quality of OI management and pave the way for the development of more inclusive health policies focused on patients with rare genetic disorders in Indonesia.

Method

The type of research conducted is a case study or a case report the patient is an 8-year-old girl referred from Bima Regional Hospital who came to the emergency room of West Nusa Tenggara Provincial Hospital with complaints of pain on the left foot since 1 week ago. Complaints of pain felt continuous, aggravated when moved, and improved at rest. The patient also complained of swelling on the left thigh since 1 week ago. The swelling was felt to be worse with movement and improved with rest. The patient complained of pain and swelling on the left thigh after falling from the gazebo when she wanted to go down and then lost her balance at a height of about 1 meter with a cement platform and fell into a sitting position 1 week ago. The patient was then carried home in a conscious state and was brought to Bima Hospital on July 22, 2024 because of complaints of worsening pain. The patient was then referred to the West Nusa Tenggara Provincial Hospital on July 24, 2024 (3 days ago) for further treatment. Complaints of fever were denied, bowel movements (defecation) and urination were normal. At home, the patient was given paracetamol for pain but there was no improvement.

Result and Discussion

The patient had experienced similar complaints before, a history of fracture at the age of 2 years on the left thigh in 2018. The patient was found to have a bone disorder when the patient's mother did an ultrasound examination of the womb during Antenatal Care (ANC). During pregnancy, the patient's mother did not suffer from any diseases. The patient was born vaginally at 42 weeks gestation with a birth weight of 2200 grams and was admitted to the Neonatal Intensive Care Unit (NICU). The patient had a history of osteogenesis imperfecta and was regularly treated at Prof. Dr. I.G.N.G. Ngoerah Hospital, Bali. History of malignancy was denied. History of surgery and allergy was denied. There were no similar complaints and no history of similar diseases in the patient's family. History of medication are paracetamol, calcium, and vitamin D. The patient currently only lives with her mother (mother has been divorced since the patient was in the womb). The patient's mother works as a housewife.

In the general status examination, it was found that the general condition was good with a Glasgow Coma Scale (GCS) E4V5M6, compos mentis consciousness, and vital signs within normal limits. General status examination on eye examination was found to have white sclera. Dental examination revealed dentinogenesis imperfecta, as shown in Figure 1. The rest of the head and neck were within normal limits. Thoracic and abdominal examinations are within normal limits.

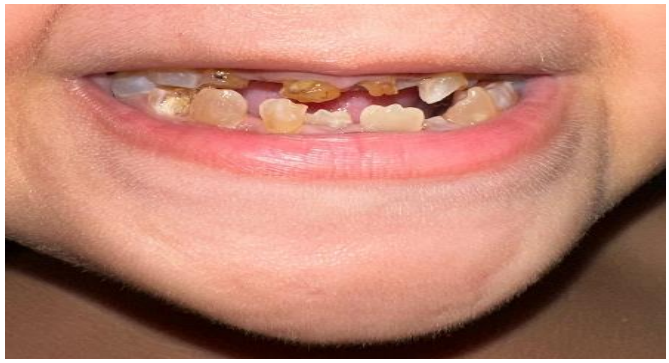

Figure 1. Dentinogenesis imperfecta

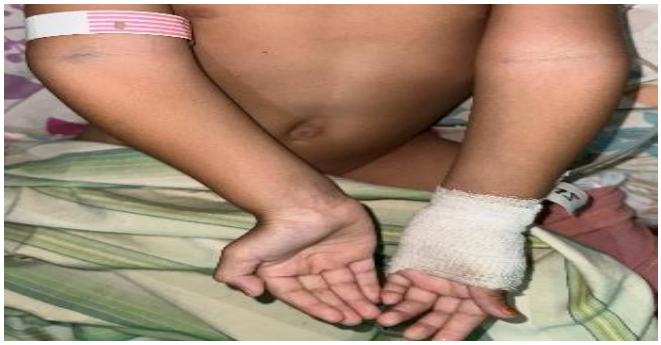

Figure 2. Varus deformity of the antebrachii region bilaterally

On examination of the local status of the superior extremities, both acrals were found to be warm,

Capillary Refill Time (CRT) <2 seconds, and varus deformity in the antebrachi region bilaterally as shown in Figure 2 (a), no tenderness was found, and active and passive range of motion (ROM) was not limited. On examination of the sinistra inferior extremity, both acrals were found to be warm, CRT <2 seconds, deformity was found in the femur region, deformity in the tibia region (there was angulation), edema was seen, no open wounds were found as in Figure 2 (b), equinus and varus deformities were seen as in Figure 3, tenderness was found, crepitation was difficult to evaluate due to pain, pulsation (posterior popliteal, posterior tibial, and dorsal pedis artery) was strong, active and passive ROM was found to have limited motion. On examination of the inferior extremities, both acrals were found to be warm, CRT <2 seconds, deformity was found in the tibia region (angulation) as in Figure 4, equinus and varus deformities were seen as in Figure 5, no tenderness and crepitation were found, pulsation (posterior popliteal, posterior tibial, and dorsal pedis artery) was strong lifting, active and passive ROM was not found to be limited in motion.

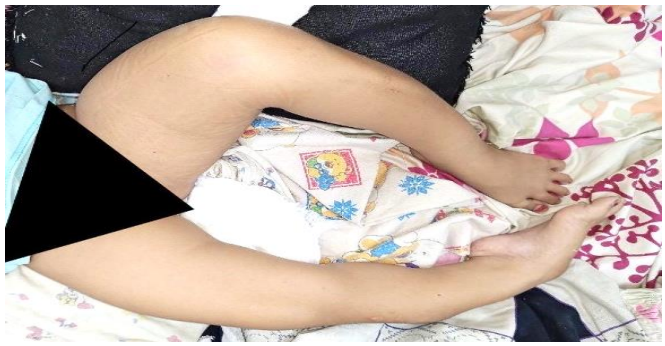

Figure 3. Deformity and edema of sinistra femur region, no open wound, deformity of tibia region (angulation) bilaterally, equinus and varus deformity bilaterally

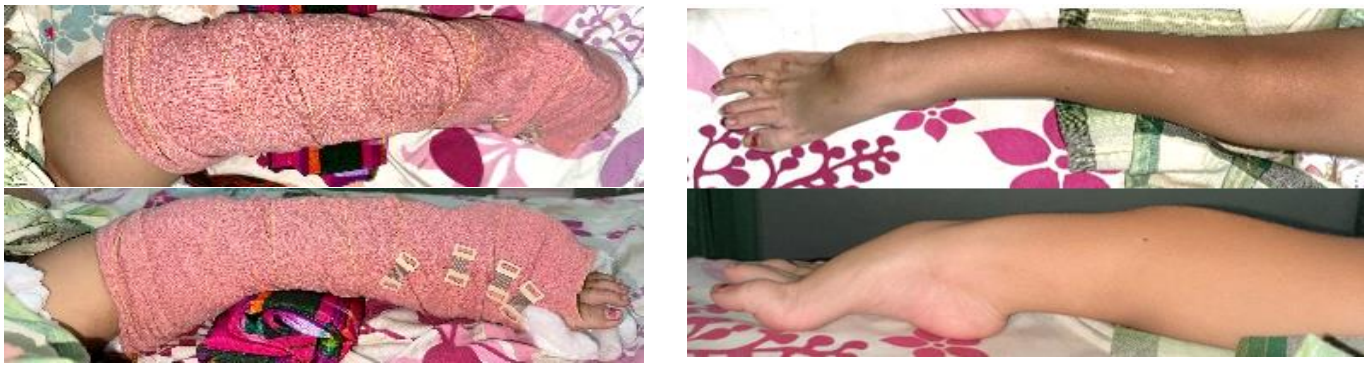

Figure 4. (a) Anterior and lateral view of the sinistra inferior limb. Deformity of the femur and tibia region (angulation), edema, equinus and varus deformity; and (b) Anterior and lateral view of the dextral inferior limb. Deformity of the tibia region (angulation)

Figure 5. Bilateral equinus and varus deformities

On laboratory examination (July 25, 2024), the calcium (Ca) level was 10.60 mg/dL (Increased, Normal: 8.60 - 19.30 mg/dL) and the total vitamin D level was 24.5 ng/mL (Insufficient) (Deficient: <20 ng/mL; Insufficient: 20 - 29 ng/mL; Sufficient: 30 - 100 ng/mL). On examination of femur plain photographs (July 22, 2024), there was an impression of a displaced complete fracture of the middle 1/3 os. femur sinistra with surrounding soft tissue edema and dislocation of the femurotibial joint sinistra, as shown in Figure 6.

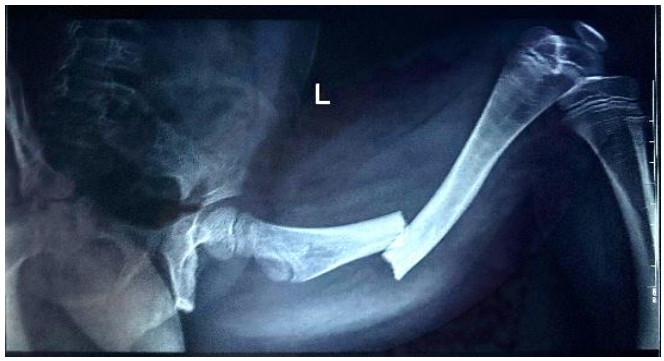

Figure 6. Plain photograph of sinistra femur anteroposterior (AP) view

The patient was assessed with closed fracture of sinistra femur, osteogenesis imperfecta, Congenital Talipes Equinovarus (CTEV). The patient has been given calcium therapy, vitamin D, paracetamol injection, and lactat ringer infusion. The patient is planned for ORIF and will be referred to Prof. Dr. I.G.N.G. Ngoerah Hospital, Bali for further treatment.

Discussion

Osteogenesis imperfecta or commonly referred to as brittle bone disease is a disorder from congenital bone fragility caused by a genetic mutation in the procollagen type 1 code. Initially, the study of osteogenesis imperfecta was carried out by Olof Jakob Ekman in 1788. In 1833, Jean Lobstein described osteogenesis imperfecta type I as a disease called Lobstein's disease. Then around the 1850s, Willem Vrolik also described it so that it is currently known as Vrolik syndrome (osteogenesis imperfecta) (Mustikasari et al., 2022; Noor, 2020; Sam & Dharmalingam, 2017).

Epidemiology

The prevalence of osteogenesis imperfecta in the world is found to be around 1:20,000 to 1:50,000 live births. The prevalence of osteogenesis imperfecta in Indonesia is still unknown. According to data from the Endocrinology Coordination Unit of IDAI (Indonesian Pediatric Association), there were 170 cases of osteogenesis imperfecta in the last 10 years with a ratio of male to female of 1:1 (Not associated with gender). The incidence of osteogenesis imperfecta is also not associated with a particular race (Wishbone Day, 2016).

Etiology

Osteogenesis imperfecta is an inherited defect caused by genetic mutations. Almost 90% of osteogenesis imperfecta types caused by a structural abnormality or abnormal production of type I procollagen (COL1A1 and COL1A2), a major protein component of the extracellular matrix of skin and bone. In 10% of clinically unclear cases, there are no molecular or biochemical abnormalities of procollagen. However, the etiology of osteogenesis imperfecta cases is unknown due to heterogeneous genetic abnormalities or limited detection (Noor, 2020).

Patophysiology

Osteogenesis imperfecta involves genetic mutations of two genes, the COL1A1 gene and COL1A2 gene which encodes the synthesis and/or post translational modification of type 1 collagen found in approximately 90% of osteogenesis imperfecta patients. COL1A1 encodes the pro-α1 chain of procollagen located on the long arm of chromosome 17, while COL1A2 encodes the pro-α2 chain of procollagen located on the long arm of chromosome 7. Both chains form a triple helix molecule which is the type 1 collagen found in bone, skin and other connective tissues that maintain the structure and strength of the body. Alterations in the COL1A1 and COL1A2 genes result in a defect in either the pro-alpha 1 or pro-alpha 2 chain which causes the production of type 1 collagen to decrease, resulting in brittle bones (Kartika & Suadiatmika, 2018; Phonela et al., 2020).

Clinical Manifestations and Diagnosis

The diagnosis of osteogenesis imperfecta is based on history taking, physical examination, and supporting examination. Based on history taking, in the prenatal history, a long bone fracture was found in the fetus in the womb during an ultrasound examination. The perinatal history was found to have frequent fractures. In the family history, there was a family history of recurrent fractures, a history of perinatal death, blue sclera in the family, early hearing loss in the family, and a family history of brittle teeth (dentinogenesis imperfecta). The history of the disease was asked about the onset of complaints, the progressiveness of the disease, the history of recurrent fractures, and the history of growth (Wishbone Day, 2016). On physical examination, the disorders that can be found depend on the severity according to the type of osteogenesis imperfecta, as shown in Table 1 and Figure 7 (Noor, 2020). Supporting examinations that can be performed include radiological examinations (signs of fracture or decreased bone mineral density (osteoporosis or osteopenia)), including bone surveys as in Figures 7, 8, 9, prenatal ultrasound as in Figure 2, and Bone Mineral Desinometry (BMD); laboratory examinations, including bone biochemical examinations (vitamin D, calcium, magnesium, alkaline phosphatase, and phosphate); and if clinical doubts remain, further examinations can be carried out, such as fibroblast culture and mutation analysis (if possible) (Wishbone Day, 2016).

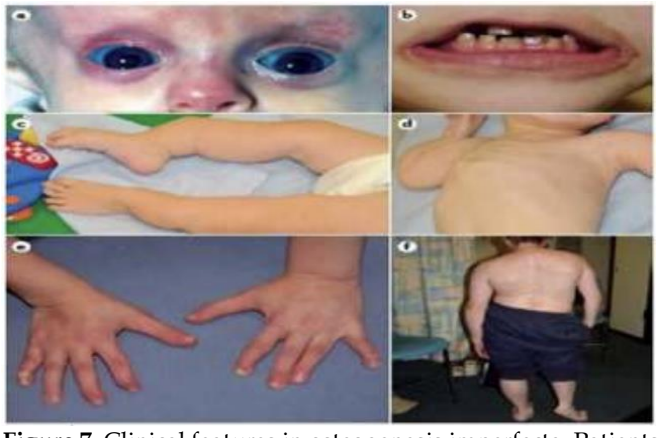

Figure 7. Clinical features in osteogenesis imperfecta. Patients with osteogenesis imperfecta may show secondary signs, such as: (a) blue sclera; (b) dentinogenesis imperfecta characterized by dentinal dysplasia, resulting in porous and discolored teeth; (c) limb deformities; (d) pectus carinatum chest deformity (known as "pigeon's chest"); (e) clinodactyly characterized by abnormal curvature of the fingers; and (f) scoliosis characterized by curvature of the spine (Mustikasari et al., 2022)

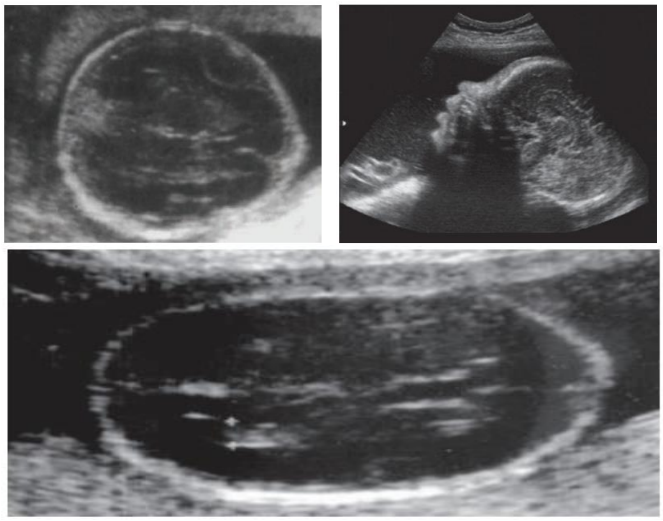

Figure 8. Images (A) and (B) show images of decreased ossification of the calvaria bone, resulting in well-visualized brain tissue (when compared to normal prenatal ultrasound). Image (C) on pressing with the transducer shows the deformity or compressed shape of the calvaria (Kartika & Suadiatmika, 2018)

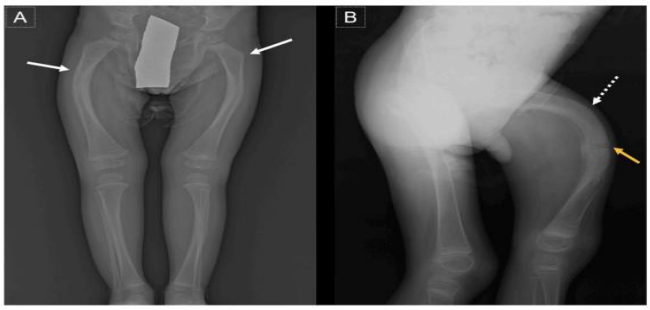

Figure 9. "Shepherd's crook" deformity of the femur. (A) Anteroposterior radiologic view of the lower limbs showing bilateral femoral "shepherd's crook" deformities (white arrows) of a 2-year-old patient with osteogenesis imperfecta. (B) Lateral view of the lower limbs of a 1-year-old patient with osteogenesis imperfecta type 3 showing "shepherd's crook" deformity of the femur (dashed arrow). There was a history of fracture of the sinistra femur (callus formation (yellow arrow)) (Gazzotti et al., 2024)

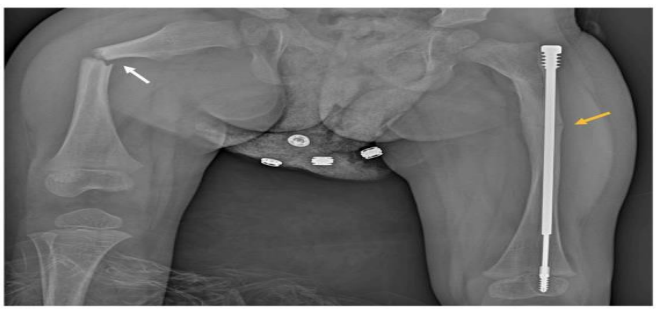

Figure 10. Bilateral femur fractures. Anteroposterior radiologic image of the pelvis shows a displaced diaphyseal fracture of the dextral femur (white arrow) of a 2-year-old patient with osteogenesis imperfecta type 3, and a history of a diaphyseal fracture of the sinistral femur (yellow arrow) with intramedullary nailing (Gazzotti et al., 2024)

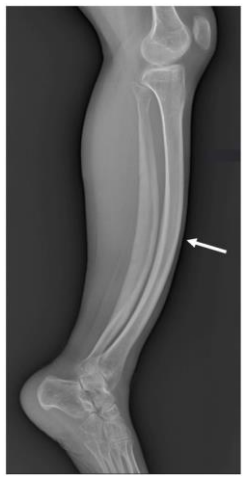

Figure 11. "Saber shin" deformity of the tibia. Lateral limb radiology shows a "saber shin" deformity (characterized by anterior bending) of the sinistra tibia (white arrow) in a 19-year-old patient with osteogenesis imperfecta. This deformity also affects the fibula (Gazzotti et al., 2024)

Management

Management of patients with osteogenesis imperfecta requires multidisciplinary care. In some cases, management needs to be started from birth, but because this disease is a disease based on genetic disorders, there is no effective management. There are several treatments that can be done, including conservative management, surgical management, and medical rehabilitation (Kresnadi et al., 2024; Noor, 2020; Ralston & Gaston, 2020).

The main goals of conservative management are to reduce fracture rates, improve functional outcomes, and prevent deformity of the long bones and scoliosis. Osteogenesis imperfecta is caused by a genetic condition, so there is no specific management that can be done (Marom et al., 2020; Rahman et al., 2023). However, some studies have shown that intravenous administration of bisphosphonates (Pamidronate) showed improvement in children with osteogenesis imperfecta. Bisphosphonate is a synthetic analogue of pyrophosphate (a natural inhibitor of osteoclastic bone reabsorption), so it can strengthen bone and increase bone mineralization by shortening the life span of osteoclasts and suppressing osteoclast activity.

Patients with osteogenesis imperfecta are also trauma-prone, requiring long-term immobilization as the fractures often result in calcium and vitamin D deficiency in children (Tandra, 2009). Therefore, management may include vitamin D supplementation of 400-800 IU and calcium of 500-1000 mg as prophylaxis (although not treating osteogenesis imperfecta itself) (Noor, 2020).

Table 1. Clinical and Types of Osteogenesis Imperfecta (Noor, 2020)

Type	Clinical
Type I	Over a lifetime, fracture incidence between 1 - 60 times Presence of dentinogenesis imperfecta Fractures are common during infancy and can occur at all age phases No deformity of long bones Blue or white sclera present Exercise tolerance and muscle strength are significantly decreased Height is generally normal Adaptability to pain is very high Other possible features: Prone to bruising, kyphoscoliosis, hearing loss, and premature senile arching
Type II	Severe deformity of long bones Protrusion of ribs Blue sclera All patients had fractures in utero, such as fractures of long bones, head bones, and vertebrae Major cause of death: Rib fractures and central nervous system malformations/hemorrhages
Type III	Has bone fragility during infancy, skull deformity, muscle weakness, joint disorders (hyperlaxity) and chronic bone pain. Has a triangular face with malocclusion. Congenital heart structure malformations. Presence of dentinogenesis imperfecta Deformity of the upper skeleton. Fracture in utero Deformity and shortening of the body frame Blue sclera color Secondary respiratory complications of kyphoscoliosis Hypercalciuria Vertigo Hernia Constipation
Type IV	Type IV is a type of osteogenesis imperfecta that is not clearly identified. Although the patient has normal sclera or height, dentinogenesis imperfecta can be found. Fractures can often occur in infancy. Long bones are generally bent.

The orthopedic surgical management that can be performed includes deformity correction and fracture treatment. Fracture management should be splinted or cast. In cases of osteogenesis imperfecta, fractures heal well and casts are used to minimize osteoporosis due to long-term immobilization. Correction of long bone deformities requires intramedullary rod placement and osteotomy procedures (Noor, 2020). The surgical management that can be performed in cases of osteogenesis imperfecta with long bone fractures includes Open Reduction Internal Fixation (ORIF), casting or splinting in younger children, and intramedullary devices (Georgiadis et al., 2024; Sheppard & Estes, 2017).

In the management of physical rehabilitation activities starting at an early age, so that patients can achieve higher functional levels, such as joint stabilization, isotonic muscle strengthening, and aerobic exercise (Arovah, 2021). Patients with type I osteogenesis imperfecta and in some cases type IV osteogenesis imperfecta can mobilize spontaneously. The majority of type III osteogenesis imperfecta patients require a wheelchair, but it still does not prevent recurrent fractures. The majority of patients with type IV osteogenesis imperfecta and some patients with type III osteogenesis imperfecta can walk or mobilize with a combination of physical therapy to increase stamina, strengthen hip joint muscles, use bracing, and orthopedic correction. Parents are instructed in the care of their child. Special attention needs to be given to various activities that can lead to traumatizing conditions, such as when wearing children's clothes, during bathing, or other physical stimulation (Noor, 2020).

Conclusion

Osteogenesis imperfecta is a disorder that cause congenital bone fragility due to genetic mutations in the procollagen type 1 code. The diagnosis of osteogenesis imperfecta is based on anamnesis, physical examination, and supporting examination. Management that can be done in patients with osteogenesis imperfecta, such as conservative management, surgical management, and medical rehabilitation. The authors declare that they have obtained all patient informed consents. In the informed consents, patients have given their consent for their clinical information and images to be reported in

the journal. The patient understands that her name and initials will not be published in order to conceal her identity, but anonymity cannot be guaranteed.

Acknowledgments
Researchers express their greatest gratitude to all parties, both from inside and outside institution.

Author Contributions
This article was written by two authors, namely I. G. B. S. M and D. P. All authors worked together at every stage of the writing of this article.

Funding
This research was independently funded by the researchers.

Conflicts of Interest
The authors declare no conflict of interest.

References

Arovah, N. I. (2021). *Olahraga Terapi Rehabilitasi pada Gangguan Musculoskeletal*. Yogyakarta: UNY Press.

Claeys, L., Storoni, S., Eekhoff, M., Elting, M., Wisse, L., Pals, G., Bravenboer, N., Maugeri, A., & Micha, D. (2021). Collagen transport and related pathways in Osteogenesis Imperfecta. *Human Genetics*, *140*(8), 1121–1141. https://doi.org/10.1007/s00439-021-02302-2

Etich, J., Rehberg, M., Eckes, B., Sengle, G., Semler, O., & Zaucke, F. (2020). Signaling pathways affected by mutations causing osteogenesis imperfecta. *Cellular Signalling*, *76*, 109789. https://doi.org/10.1016/j.cellsig.2020.109789

Forlino, A., & Marini, J. C. (2016). Osteogenesis imperfecta. *The Lancet*, *387*(10028), 1657–1671. Retrieved from https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)00728-X/abstract

Gazzotti, S., Sassi, R., Aparisi Gómez, M. P., Moroni, A., Brizola, E., Miceli, M., & Bazzocchi, A. (2024). Imaging in osteogenesis imperfecta: Where we are and where we are going. *European Journal of Medical Genetics*, *68*, 1–14. https://doi.org/10.1016/j.ejmg.2024.104926

Georgiadis, A. G., Pottinger, T. J., Sigrist, E. J., & Truong, W. H. (2024). Iatrogenic Intraoperative Fracture in Patients With Osteogenesis Imperfecta. *Journal of Pediatric Orthopaedics*, *44*(10), e945--e950. https://doi.org/10.1097/BPO.0000000000002778

Ghandforoushan, P., Alehosseini, M., Golafshan, N., Castilho, M., Dolatshahi-Pirouz, A., Hanaee, J., Davaran, S., & Orive, G. (2023). Injectable hydrogels for cartilage and bone tissue regeneration: A review. *International Journal of Biological Macromolecules*, *246*, 125674. https://doi.org/10.1016/j.ijbiomac.2023.125674

Kartika, & Suadiatmika, D. G. M. (2018). Gambaran Radiologi untuk Deteksi Prenatal Osteogenesis Imperfecta. *Cermin Dunia Kedokteran*, *45*(6), 446–448. https://doi.org/10.55175/cdk.v45i6.771

Kresnadi, A., Martanto, T. W., Zulkarnain, A., & Yazid, H. (2024). The Role of Denosumab and Bisphosphonate in Osteogenesis Imperfecta: A Literature Review. *Salud, Ciencia y Tecnología*, *4*, 894. https://doi.org/10.56294/saludcyt2024894

Lim, J., Grafe, I., Alexander, S., & Lee, B. (2017). Genetic causes and mechanisms of osteogenesis imperfecta. *Bone*, *102*, 40–49. https://doi.org/10.1016/j.bone.2017.02.004

Liu, Y., Zhu, Z., Pei, X., Zhang, X., Cheng, X., Hu, S., Gao, X., Wang, J., Chen, J., & Wan, Q. (2020). ZIF-8-Modified Multifunctional Bone-Adhesive Hydrogels Promoting Angiogenesis and Osteogenesis for Bone Regeneration. *ACS Applied Materials & Interfaces*, *12*(33), 36978–36995. https://doi.org/10.1021/acsami.0c12090

Marini, J. C., & Cabral, W. A. (2018). *Osteogenesis Imperfecta* (pp. 397–420). Academic Press. https://doi.org/10.1016/B978-0-12-804182-6.00023-X

Marom, R., Rabenhorst, B. M., & Morello, R. (2020). Management of endocrine disease: Osteogenesis imperfecta: An update on clinical features and therapies. *European Journal of Endocrinology*, *183*(4), R95--R106. https://doi.org/10.1530/EJE-20-0299

Morello, R. (2018). Osteogenesis imperfecta and therapeutics. *Matrix Biology*, *71*, 294–312. https://doi.org/10.1016/j.matbio.2018.03.010

Mustikasari, R. I., Rochmah, N., Faizi, M., & Putri, Q. A. N. (2022). Osteogenesis Imperfecta: An Overview Rahma. *International Journal Of Scientific Advances*, *3*(3). https://doi.org/10.51542/ijscia.v3i3.9

Noor, Z. (2020). Gangguan Kongenital. In *Buku Ajar Gangguan Muskuloskeletal* (pp. 94–102). Salemba Medika.

Phonela, S., Goller, R., & Karsas, M. (2020). Osteogenesis imperfecta: an overview. *South African Orthopaedic Journal*, *19*(4), 229–234. https://doi.org/10.17159/2309-8309/2020/v19n4a6

Pulungan, A. B., Batubara, J. R., Tridjaja, B., Soesanti, F., Fadiana, G., Mada, S. I., & Annisa, D. (2019). Clinical Profile and IV Bisphosphonate Therapy in Children with Osteogenesis Imperfecta in Cipto Mangunkusumo Hospital. *Asia Pasidic Journal of Pediatrics and Child Health*, *3*, 13–23. Retrieved from https://apjpch.com/pdfs/19213XRN034712.pdf

Rahman, F. U. A., Hidayat, M. F., Yunus, B., & Syahrir, S. (2023). Osteogenesis imperfecta in incidental findings of panoramic radiographic examination.

Makassar Dental Journal, *12*(3), 391–393. https://doi.org/10.35856/mdj.v12i3.855

Ralston, S. H., & Gaston, M. S. (2020). Management of osteogenesis imperfecta. *Frontiers in Endocrinology*, *10*, 924. https://doi.org/10.3389/fendo.2019.00924

Rauch, F., & Glorieux, F. H. (2004). Osteogenesis imperfecta. *The Lancet*, *363*(9418), 1377–1385. https://doi.org/10.1016/S0140-6736(04)16051-0

Sam, J., & Dharmalingam, M. (2017). Osteogenesis Imperfecta. *Indian Journal of Endocrinology and Metabolism*, *21*(6), 903–908. https://doi.org/10.4103/ijem.IJEM_220_17

Sheppard, E., & Estes, R. (2017). Osteogenesis Imperfecta. In *Orthopedic Surgery Clerkship* (pp. 553–555). Springer International Publishing. https://doi.org/10.1007/978-3-319-52567-9_116553

Shih, C.-A., Li, C.-C., Chang, Y.-F., Hwang, J.-S., Tsai, M.-C., Chou, Y.-Y., Lin, C.-J., Huang, M.-T., Hong, C.-K., Tai, T.-W., & others. (2024). Demographics and medical burden of osteogenesis imperfecta: a nationwide database analysis. *Osteoporosis International*, 1–9. https://doi.org/10.1007/s00198-024-07051-2

Syafira, I. (2019). *Analisis Faktor Yang Memengaruhi Terjadinya Osteoporosis pada Ibu Menopause di Wilayah Kerja Puskesmas Stabat Kabupaten Langkat Tahun 2019* [Thesis: Institut Kesehatan Helvetia]. Retrieved from https://repository.helvetia.ac.id/id/eprint/2813

Tandra, H. (2009). *Segala sesuatu yang harus anda ketahui tentang osteoporosis: mengenal, mengatasi, dan mencegah tulang keropos*. Jakarta: PT Gramedia Pustaka Utama.

Trejo, P., & Rauch, F. (2016). Osteogenesis imperfecta in children and adolescents—new developments in diagnosis and treatment. *Osteoporosis International*, *27*(12), 3427–3437. https://doi.org/10.1007/s00198-016-3723-3

Verdonk, S. J. E., Storoni, S., Micha, D., van den Aardweg, J. G., Versacci, P., Celli, L., de Vries, R., Zhytnik, L., Kamp, O., Bugiani, M., & others. (2024). Is osteogenesis imperfecta associated with cardiovascular abnormalities? A systematic review of the literature. *Calcified Tissue International*, *114*(3), 210–221. https://doi.org/10.1007/s00223-023-01171-3

Whyte, M. P. (2017). Hypophosphatasia: An overview For 2017. *Bone*, *102*, 15–25. https://doi.org/10.1016/j.bone.2017.02.011

Wishbone Day. (2016). *Mengenal Osteogenesis Imperfecta, Kelainan Tulang Rapuh dan Mudah Patah* (pp. 1–7). Ikatan Dokter Anak Indonesia. Retrieved from https://www.idai.or.id/artikel/seputar-kesehatan-anak/mengenal-osteogenesis-imperfecta-kelainan-tulang-rapuh-dan-mudah-patah