Case Report

Osteogenesis Imperfecta: Bridging Genetic Insights with Clinical Signs

Udi H. Hancoro,[1,2] Marsa Zaidan,[2*] Hikam Y. Pradana,[2] Alson B. Timotius[2]

[1]Pediatric Orthopaedic and Traumatology Department Faculty of Medicine, Sebelas Maret University – Dr. Moewardi General Hospital, Surakarta, Indonesia
[2]Faculty of Medicine Sebelas Maret University – Dr. Moewardi General Hospital, Surakarta, Indonesia

*Corresponding author: marsazaidan8@gmail.com
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Abstract

Osteogenesis Imperfecta (OI) is a rare genetic disorder affecting collagen production, leading to bone fragility and fractures. This case report aims to highlight the challenges and advancements in managing this condition. This report presents a rare case of a 13-year-old boy with OI, who experienced multiple fractures from minimal trauma, leading to mobility challenges. The patient first presented to Dr. Moewardi General Hospital, Surakarta, in June 2021, seeking evaluation for multiple bone fractures and mobility issues. Despite the absence of typical blue sclerae, the patient exhibited other OI symptoms such as dental growth disorders and a history of nine bone surgeries. Physical examination revealed bowing of the right lower limb and abnormal gait, while radiological findings confirmed bone deformities and fractures. OI results from mutations in the COL1A1 and COL1A2 genes, which are crucial for type I collagen synthesis. These genetic mutations lead to reduced bone density and increased fracture susceptibility. While clinical presentations vary, this patient did not exhibit blue sclerae or hearing loss. Diagnosis involves clinical and radiographic assessments, with bisphosphonates used for managing symptoms. OI remains a rare genetic disorder due to infrequent mutations in collagen-related genes. While bisphosphonates provide symptomatic relief, they do not cure the disease, highlighting the need for further research into treatments targeting the genetic etiology of OI.
Keywords: *osteogenesis imperfecta, brittle bone, fragile bone, bone disease.*

Osteogenesis Imperfecta: Menghubungkan Wawasan Genetik dengan Tanda Klinis

Abstrak

Osteogenesis Imperfecta (OI) adalah kelainan genetik langka yang memengaruhi produksi kolagen, yang menyebabkan kerapuhan tulang. Laporan kasus ini bertujuan untuk menunjukkan metode dan kemajuan penanganan kondisi ini. Laporan ini menyajikan kasus langka seorang anak laki-laki berusia 13 tahun dengan OI, yang mengalami beberapa patah tulang akibat trauma ringan, yang menyebabkan gangguan mobilitas. Pasien pertama kali datang ke RSUD Dr. Moewardi, Surakarta pada bulan Juni 2021 untuk menjalani evaluasi terhadap keluhan patah tulang berulang dan masalah mobilitas. Meskipun tidak ada sklera biru yang khas, pasien menunjukkan gejala OI lainnya seperti gangguan pertumbuhan gigi dan riwayat sembilan kali operasi patah tulang. Pemeriksaan fisik menunjukkan tungkai kanan bawah bengkok dan gaya berjalan yang tidak normal, sementara temuan radiologis mengkonfirmasi adanya kelainan bentuk tulang dan patah tulang. OI diakibatkan oleh mutasi pada gen COL1A1 dan COL1A2, yang sangat penting untuk sintesis kolagen tipe I. Mutasi genetik ini menyebabkan berkurangnya kepadatan tulang dan meningkatnya kerentanan patah tulang. Meskipun presentasi klinisnya bervariasi, pasien ini tidak menunjukkan sklera biru atau gangguan pendengaran. Diagnosis melibatkan penilaian klinis dan radiografi, dengan bifosfonat yang digunakan untuk menangani gejala. OI merupakan kelainan genetik yang jarang terjadi karena mutasi yang terjadi pada gen yang berhubungan dengan kolagen. Meskipun bifosfonat dapat meredakan gejala, obat ini tidak dapat menyembuhkan penyakit, sehingga perlu dilakukan penelitian lebih lanjut mengenai pengobatan yang menargetkan etiologi genetik OI.
Kata kunci: *Osteogenesis imperfecta, brittle bone, fragile bone, bone disease.*

Introduction

Osteogenesis imperfecta (OI) or brittle bone disease is a rare hereditary condition affecting connective tissues, resulting from a disorder in the production or modification of type I collagen.[1] The condition is mostly passed down by autosomal dominant inheritance, however there have been documented cases of autosomal recessive variants.[2] Bone fragility, a high frequency of fractures, bone deformities, and a growth deficiency are the defining characteristics of OI.[1] Osteogenesis imperfecta has a prevalence of 5 in 100,000 live birth without gender limitations or equals and affects individuals of all races and ethnicities.[3] This case is being reported due to its rarity, with the intention of reviewing the literature to emphasise the challenges and advancements in its management. The patient first presented to Dr. Moewardi General Hospital, Surakarta, in June 2021, seeking evaluation for multiple bone fractures and mobility issues.

Case Description

This is a rare case of a 13-year-old boy who was referred to the Department of Orthopaedics with the chief complaint of pain leg. The patient felt pain in the leg after falling at home. On physical examination the patient displayed abnormal development such as, disproportionate legs bones that are bent to outwards (bow legs). His medical history indicated that he had sustained multiple fractures during routine treatment, which resulted in difficulty walking. The patient had regular physiotherapy at the hospital. There were no abnormalities in the patient's pregnancy history, routine check-ups at the health center and ultrasounds from specialist doctors. The patient was born at the 32nd week of gestation with a birth weight of 2500g. At this age, the patient has good cognitive abilities.

Therefore, patient have an abnormal gait. In the swollen area, the consistency is soft, fluctuating, and warm on palpation. The patient has a history of 9 bone fracture operations. The patient's profile has a round face. The patient has a blue sclera appearance. The patient exhibited blue sclerae since birth, whereas symptoms of bone deformity and increased susceptibility to fractures developed at the age of seven years (Figure 1). The patient first visited a clinic in June 2021 and was immediately referred to Dr. Moewardi General Hospital for further diagnostic evaluation and management.

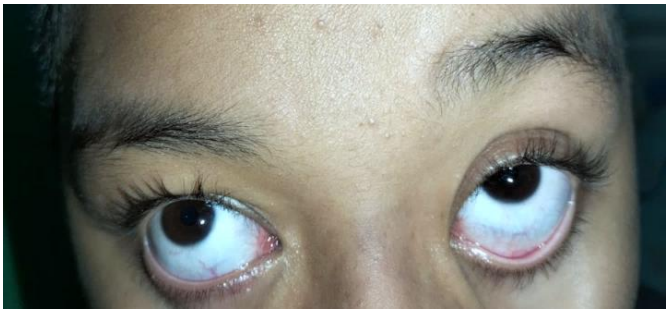

Figure 1. Blue Sclera Appearance

During the intraoral examination, a missing tooth was found on the 2nd upper right molar, 1st upper right canine, 1st upper left incisor and 2nd lower left molar which was tender on percussion but still strong and rubbery and the teeth were uneven. Tooth present was molar 1 upper right, canines upper right, incisor 2 upper right, incisor 1 upper right, incisor 2 lateral upper left, canines upper left, molar 1 upper left, molar 2 upper left, molar 1 lower right, molar 2 right lower, lower right canines, lower right 2nd incisor, lower right 1st incisor, lower left 1st incisor, lower left 2nd incisor, lower left canines, lower left 1st molar (Figure 2).

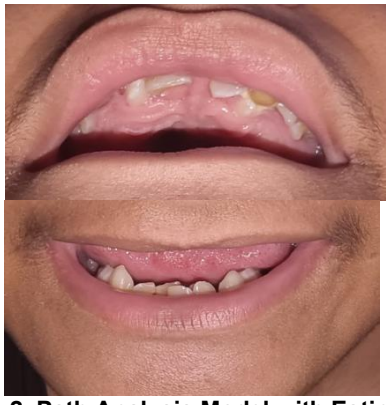

Figure 2. Path Analysis Model with Estimation

The measurements of the patient on admittance to hospital here: Height: 128 cm; body weight 43 kg, body mass index 26.2 kg/m2; and head circumference 51 cm. The height data at his age according to the CDC table is below the 5th percentile. Over the past 6 years, the patient had a height increase of 17 cm. Every 3-month measurement data showed that the patient's height was below the 5th percentile.

The patient had undergone a total of nine surgical procedures between 2021 and 2024. On x-ray examination was performed in August 2022, x-ray of the leg region showed a fracture femur and ORIF surgery was applied. An x-ray evaluation was conducted after 2 weeks, an union appearance was obtained but the femur bone still appeared bowing, bone trabeculation outside the normal lesion, and soft tissue swelling. On X-ray examination of the antebrachii, bowing and fractures were found in the proximal ⅓ of the ulna and the medial ⅓ of the left radius accompanied by soft tissue swelling (Figure 3). On X-ray examination of the cruris dextra, it was found that the callus formation was union due to a history of fracture. Calcium and vitamin D administration has been carried out, and the patient is currently taking bisphosphonates. In this case, genetic testing to confirm the specific underlying mutation of osteogenesis imperfecta was not performed due to the limited availability and high cost of genetic analysis, as well as the established clinical and radiological diagnosis based on characteristic findings.

Differential diagnoses for osteogenesis imperfecta include child abuse, rickets, osteomalacia, Ehlers-Danlos syndrome, idiopathic juvenile osteoporosis, and other rare skeletal dysplasias. In this patient, other diagnoses were excluded based on the presence of classical features such as blue sclerae, recurrent low-trauma fractures, early onset of symptoms, and absence of biochemical abnormalities or clinical signs suggestive of alternative metabolic bone diseases or connective tissue disorders

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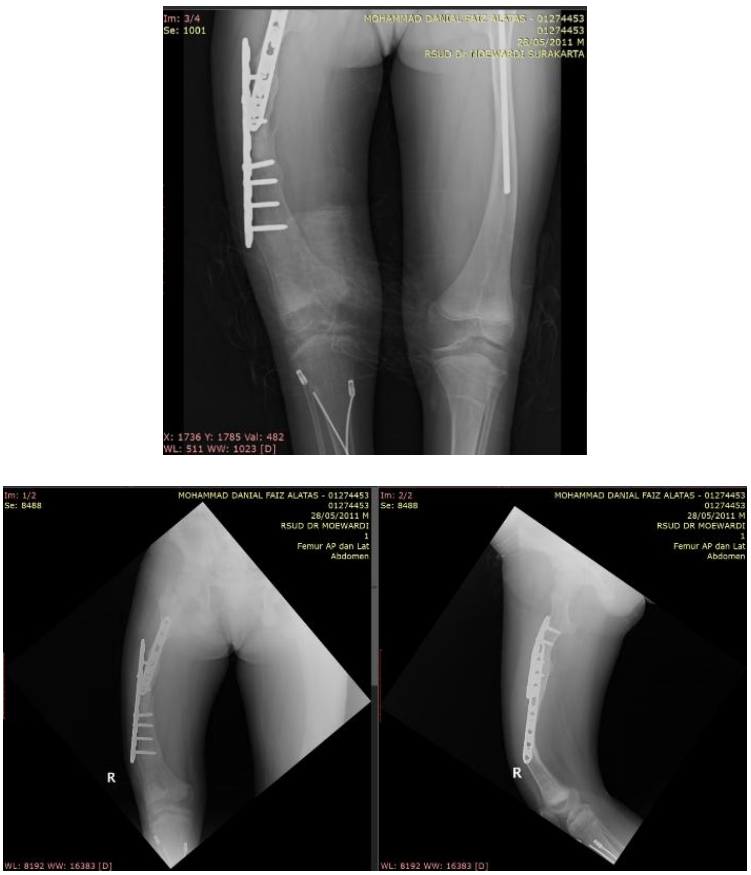

Figure 3. **Bow Bone Reoccurence after ORIF**

Discussion

Osteogenesis Imperfecta (OI) is a rare hereditary illness that includes a connective tissue disorder primarily characterized by frail body, fragility of the bones, hypermobility with easy dislocation of the joints, and blue sclerae and It's also referred to as brittle bone disease.[4,5] It is distinguished by a predisposition to bone fractures, which can range of severity from small fractures to fetal fractures.[6] Osteogenesis imperfecta results from mutations in genes encoding for type I collagen. Collagen is the major structural protein in bone, ligaments, tendons, skin, sclera, and dentin. Mutant expression produces non-functional collagen (severe OI) or insufficient quantities of collagen (mild OI).[6]

The incidence of OI varies widely but is generally estimated to occur in approximately 1 in 10,000 to 20,000 live births.[1] In indonesia According to a study from Universitas Sumatera Utara, the estimated prevalence of OI in Indonesia is approximately 1 in 15,000 births and according A report from Universitas Airlangga notes that the global incidence of OI ranges from 1 in 20,000 to 1 in 50,000 live births, which can be indicative of similar rates in Indonesia.[7] Osteogenesis imperfecta (OI) is classified as a rare disorder largely because it is caused by hereditary factors and involves distinct pathophysiological pathways. The infrequency of Osteogenesis Imperfecta (OI) is mostly linked to the mutations in the COL1A1 and COL1A2 genes, which affect the synthesis of type I collagen, a vital protein for bone integrity and architecture. These mutations are rare in the general population, resulting in the illness occurring infrequently.[1]

The severity and presentation of this condition can vary substantially among individuals, resulting in a diverse array of clinical manifestations. OI is characterized by an elevated susceptibility to fractures, which frequently occur with minimal or no trauma as a result of a reduction in bone density and structural integrity.[8] Blue sclerae, a common diagnostic indicator, are a distinctive characteristic of OI. This condition is characterized by a bluish tinge to the whites of the eyes. Furthermore, individuals with OI may experience dentinogenesis imperfecta, which results in discoloration, translucency, and fragility of the teeth, rendering them susceptible to attrition and fracturing. Another prevalent symptom is progressive hearing loss, which frequently manifests in maturity and is typically caused by abnormalities in the bones of the middle ear.[8] Growth deficiency is a common secondary feature of OI and is primarily due to the growth failure of the defective bony matrix. In our patient, there was a surgical history 9 times bone fracture without severe contact trauma. In addition, our patient have blue sclera but did not have hearing loss. However, the patient admitted that there was tooth growth disorder since infancy and our patient had developmental failure characterized by a history of height below the 5th percentile when measured by the CDC table.[8]

Osteogenesis imperfecta can be tricky to diagnose. It is possible to mix up certain primary skeletal abnormalities with osteogenesis imperfecta. The clinical diagnosis of Osteogenesis Imperfecta is based on the history, lumbar spine bone mineral density (BMD), radiographic finding, and clinical features outlined above but genetic testing can may establish the exact cause of the disease, thus confirmed by a positive collagen type 1 which associated with low bone mass but in this study it's a limitation.[9] The timing of diagnosis varies according to the severity of OI; it can be during pregnancy, at birth, in childhood, or in adulthood. Presence or absence of blue or grey sclera and dentinogenesis imperfecta as diagnostic signs of osteogenesis imperfecta in healthy infants. Hearing loss is reported half of patients older than age 50 years.[9] Diagnosis of osteogenesis imperfecta is straightforward in individuals with a positive family history or in whom several typical features are present. If we didn't find a family history, type 1 collagen analysis is very useful. We diagnosed our patient based on the patient's history of recurrent fractures in the absence of severe contact trauma. In addition, there was dental growth restriction in the patient. Although there was no blue sclera, hearing loss, and no genetic testing, we did find a lack of calcium in the patient's bones.

Gold standard of pharmacologic approach to treat OI is bisphosphonates. Bisphosphonates have been demonstrated to reduce the incidence of bone pain and fractures in certain studies. Nevertheless, their efficacy in enhancing bone quality and alleviating bone pain is limited to a duration of one year.[10] As in the case of our patient, bisphosponate was administered, but this only relieved the patient's pain without eliminating the etiology, resulting in the patient still experiencing recurrent fractures to date.

Osteogenesis imperfecta is a rare case with a prevalence of 1 in 20,000 population. The disease is rare due to rare mutations in the COL1A1 and COL1A2 genes. Currently, the gold standard treatment is the administration of bisphosphonates. This can relieve the pain experienced by the patient, but does not eliminate the existing etiology so it is a challenge for further research to develop treatments that can overcome the etiology that causes osteogenesis imperfecta.

Conclusion

Osteogenesis Imperfecta (OI) remains a complex and challenging condition to manage, requiring a multidisciplinary approach to care. Continued research into the genetic and molecular mechanisms underlying OI is essential to develop more effective therapies. Clinicians should suspect OI in cases of recurrent fractures and bone deformities, while researchers and educators should focus on developing targeted therapies that address the root cause of OI, such as gene therapy or collagen-enhancing drugs. Early diagnosis and a multidisciplinary approach are essential for improving patient outcomes.

Conflict of Interest

There are no conflicts of interest in this study.

Consent Form

Include the manner and form of consent given by the patient verbal to parents.

Acknowledgement

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