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Diagnosis of Osteogenesis Imperfecta in 23 Years Old Man: A Case Report

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ABSTRACT

Osteogenesis imperfecta is a disorder of the formation of collagen tissue that functions as connective tissue and is caused by a gene mutation that causes disturbances in the formation of type 1 collagen. This study aimed to describe the diagnosis of osteogenesis imperfecta. A 23-year-old man came to the rheumatology polyclinic of Dr. Mohammad Hoesin General Hospital Palembang with a complaint of recurrent fractures since ± 17 years ago. The patient also complained that the hearing in the left ear was slowly decreasing. The patient's right thigh was still pinned 2 years ago, but after being controlled by orthopedics, it was said that the bones were still not fused. Then the patient was referred to the rheumatology polyclinic for further examination and management. On examination, the patient was 145 cm tall and weighed 40 kg. He had blue-gray sclera, triangular facial appearance, right leg length 86 cm, left leg length 78 cm, blue sclera, and scoliosis, while secondary sex growth was within normal limits. From the examinations of bone survey and bone age, it was found osteoporotic bone structure, scoliosis, plate-screw in the middle 1/3 of the right femur, fracture union of the femur, bowing of the left femur, BMD Z-Score -3.0 means very low compared to the same age and gender. Management is more focused on supportive therapy with the aim of minimizing the occurrence of fractures, minimizing disability, and helping people with osteogenesis imperfecta to be independent and maintain overall health. The goal of orthopedic management is to treat osteogenesis imperfecta with fractures and prevent or correct bone deformity. In conclusion, osteogenesis imperfecta is a complex hereditary disease characterized by striking clinical variability necessitating a logical classification system. Disease management requires multidisciplinary experts and further research on therapeutic approaches such as bisphosphonates.

1. Introduction

Osteogenesis imperfecta (OI) is a disease characterized by increased bone fragility, low bone mass, and other connective tissue manifestations, so individuals suffering from this disease have a tendency to experience multiple fractures due to mild to moderate trauma.[1] Osteogenesis imperfecta is a rare disease with an incidence of 1 in 20,000 births. The population frequency of type I osteogenesis imperfecta ranges from 2.35 to 4.7 in 100,000 births worldwide. The reported incidence of type II osteogenesis imperfecta ranges from 1 in 40,000 to 1.4 in 100,000 live births. The exact incidence of types III and IV is unknown, although they are much less common than types I.[2] Osteogenesis imperfecta is genetically inherited. In more than 90% of people with osteogenesis imperfecta, there are mutations in the genes encoding type 1 collagen, namely COL1A1, and COL1A2, causing changes in the formation and stability of collagen, which functions as connective tissue.[3] This disorder is inherited in an autosomal

dominant, autosomal dominant mutation pattern. Recessive or spontaneous. The autosomal dominant form causes defects in the quantity or structure of type 1 collagen, whereas the autosomal recessive form causes deficiencies in proteins that interact with collagen and affect post-translational modification or folding.[4]

Patients with milder osteogenesis imperfecta generally have normal collagen, albeit in reduced amounts, whereas patients with more severe osteogenesis imperfecta generally have collagen abnormalities, defects in collagen metabolism, or osteoblast-associated pathway abnormalities.[5] The degree of bone fragility ranges from degree mild, namely occasional fractures and minimal effect on the shape or length of the bones, to severe degrees, namely progressive severe deformation with many fractures, which can exceed 200 fractures during childhood.[6] Genetic mutations that occur not only manifest as bone fragility but also in the form of skin thinning, bone structure deviation, joint hypermobility, hearing loss, tooth fragility, and blue sclera.[7,8] The diagnosis of osteogenesis imperfecta is established based on anamnesis, including family history, clinical manifestations, and supporting examinations which include radiological and laboratory examinations, and if possible, fibroblast culture and mutation analysis. This study aimed to describe the diagnosis of osteogenesis imperfecta.

2. Case Presentation

A 23-year-old man came to the rheumatology polyclinic of Dr. Mohammad Hoesin General Hospital Palembang with a complaint of recurrent fractures since ± 17 years ago. He also has impaired height growth since ± 15 years ago. From the history of the disease, there were complaints of recurrent fractures in the right and left thighs, even with minimal trauma. The left thigh had a pen and cast installed, which resulted in a fractured bone that had to be removed a few centimeters which resulted in the patient's left leg being shorter than the right leg. Patients also complain of short stature compared to most people. There are complaints of broken teeth while eating. The patient also complained that the hearing in the left ear was slowly decreasing. The patient's right thigh was still pinned 2 years ago, but after being controlled by orthopedics, it was said that the bones were still not fused. Then the patient was referred to the rheumatology polyclinic for further examination and management.

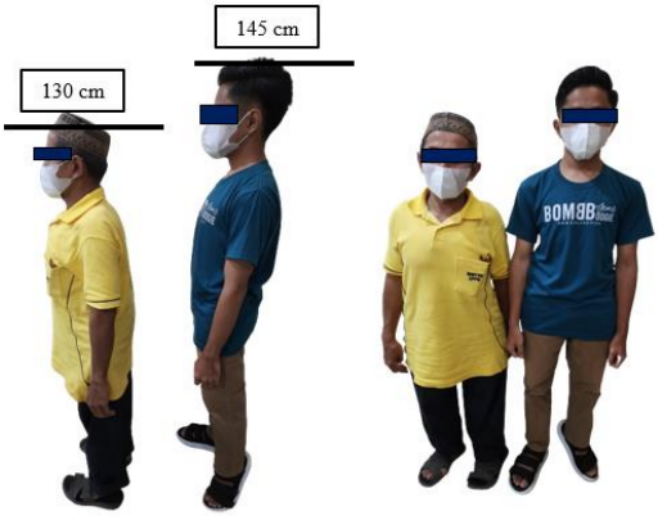


Figure 1. Patient and his father. The patient was 145 cm, and the patient's father was 130 cm.

From the past medical history, the patient often cried from a few moments to a few weeks after birth with a swollen, reddish left thigh and cried again when the left leg was moved. From a family history, the patient's father and younger brother had complaints of frequent fractures (Figure 1). The patient's father, grandfather's younger brother, and the patient's younger brother were all short in stature. The patient's younger sibling regularly goes to the children's polyclinic with complaints of frequent broken bones and is given intravenous drugs for bones every 6 months.

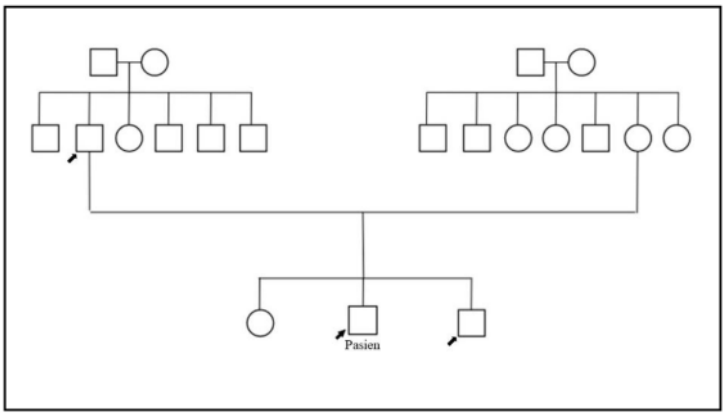


Figure 2. Pedigree chart.

On examination, the patient was 145 cm tall and weighed 40 kg. He had triangular facial appearance (Figure 3), blue-gray sclera (Figure 4), right leg length 86 cm, left leg length 78 cm, and scoliosis, while secondary sex growth within normal limits. From the examinations of bone survey and bone age, it was found osteoporotic bone structure, scoliosis, plate-screw in the middle 1/3 of the right femur (Figure 5), fracture union of the femur, bowing of the left femur, BMD Z-Score -3.0 means very low compared to the same age and gender (Figure 6). Laboratory finding was on normal limit. Growth hormone, LH, FSH also in normal limit. Vitamin D 25-OH level was 22.1 mIU/mL. The patient was diagnosed with osteogenesis imperfecta, dextra fracture femur union, lower limb-length discrepancy, and vitamin D insufficiency.

Figure 3. Triangular facial appearance.

Figure 4. Blue-gray sclera.

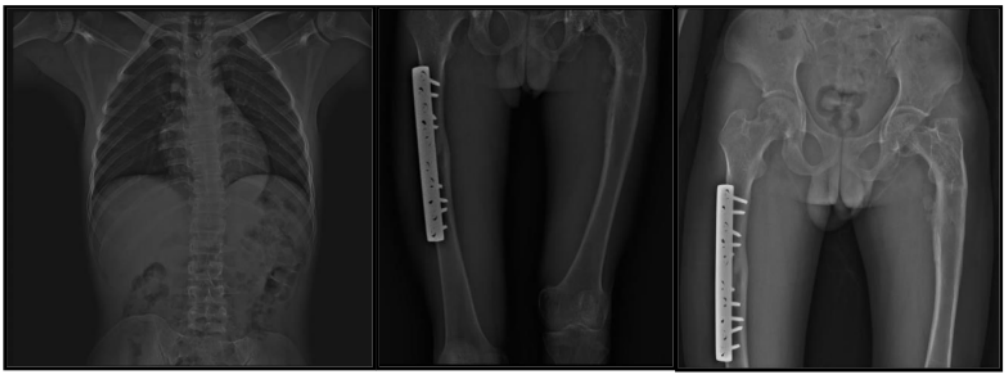
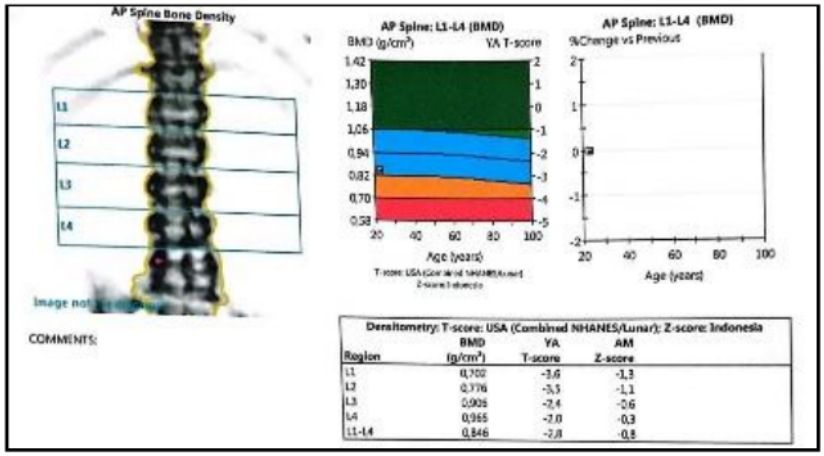


Figure 5. X-ray imaging of right and left femur bones. The patient has osteoporotic bone and scoliosis. There is a plate screw in the middle 1/3 of the right femur. Femoral fracture union. Left femoral bowing.



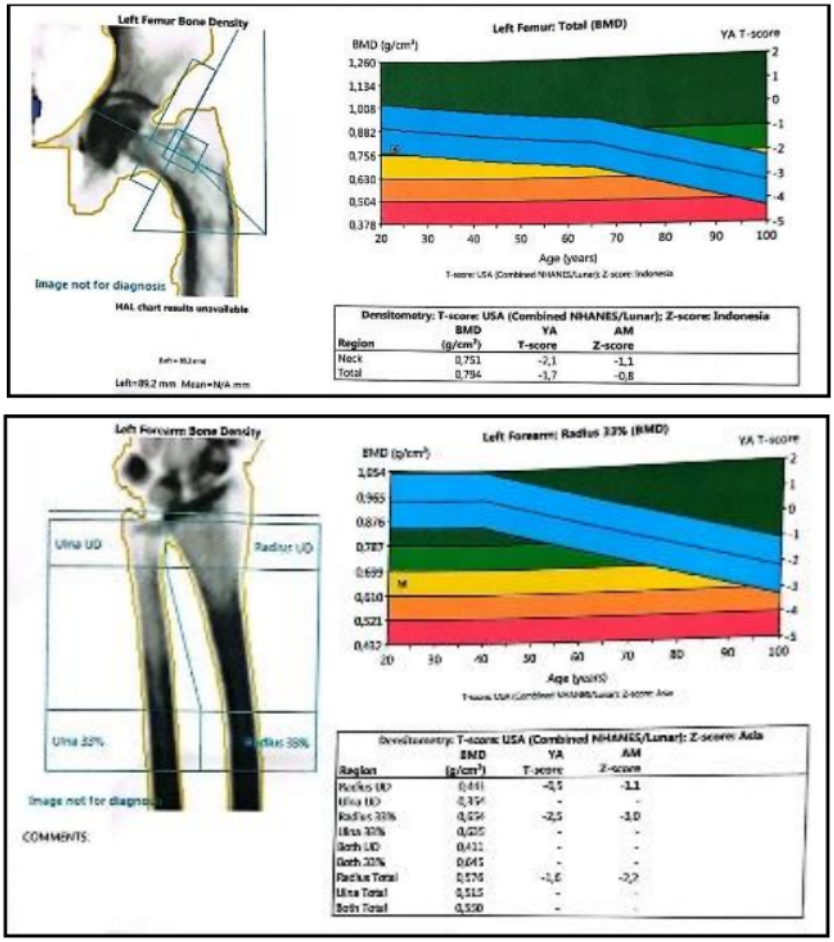


Figure 6. Bone mineral density examination (BMD). Z-Score -3.0 is very low compared to the same age and gender.

3. Discussion

Osteogenesis imperfecta is a disorder of the formation of collagen tissue that functions as connective tissue and is caused by a gene mutation that causes disturbances in the formation of type 1 collagen.[5] Type I collagen is the principal structural protein that makes up the matrix of bone and other fibrous tissues, such as organ capsules, fascia, cornea, sclera, tendons, meninges, and dermis. About 30% of the human body weight consists of type I collagen. Abnormal collagen will form an abnormal mold so that the matrix that attaches bones is not normal and is arranged irregularly. Some non-collagen proteins from the bone matrix are also reduced. This causes a decrease in bone formation, osteopenia, and fragility occurs, thus increasing the fracture rate.[5,8]

More than 200 different mutations affecting the synthesis or structure of type I collagen have been found in people with osteogenesis imperfecta. If the mutation reduces the production/synthesis of type I collagen, a mild phenotypic osteogenesis imperfecta occurs (type I osteogenesis imperfecta), but if the mutation causes a type I collagen structure disorder, then a more severe phenotypic osteogenesis imperfecta will occur (types II, III, and IV). The structural abnormalities are basically divided into two types, namely 85% due to point mutations due to glycine being replaced by other amino acids and the rest due to single exon splicing abnormalities. The normal structure of type I collagen, each collagen chain as a procollagen triple helix, is secreted into the extracellular space. The amino- and

carboxyl-terminal domains are broken down in the extracellular space, mature, then assembled in the bone. They will undergo mineralization.[8]

The first basis of OI evaluation is anamnesis, prenatal and perinatal history, family history, medical history, physical examination, appropriate radiological examination, and laboratory examinations. In the anamnesis, a history of repeated fractures with minimal triggering trauma can be found. There may also be a prenatal history of long bone fractures in the fetus on an ultrasound. In the family history, perinatal death can be found, and there are families with recurrent fractures, brittle teeth (dentinogenesis imperfecta), blue sclera, and early hearing loss.[9] A physical examination can be performed to assess the type and type of osteogenesis imperfecta. Fracture and osteopenia are clinical features of osteogenesis imperfecta. On physical examination, short stature, triangular–shaped face, respiratory problems, hearing loss, thinning of the skin, joint hypermobility, hearing loss, brittle teeth, blue sclera, and bone deformities such as crooked legs and scoliosis can be found.[10] Radiological examinations that can be performed include prenatal ultrasound, bone survey, and BMD. The examination may reveal signs of fracture or decreased bone mineral density (osteopenia or osteoporosis). Laboratory tests that can be done are bone biochemistry (calcium, vitamin D, phosphate, alkaline phosphatase, magnesium).[11]

Management is more focused on supportive therapy with the aim of minimizing the occurrence of fractures, minimizing disability, and helping people with osteogenesis imperfecta to be independent and maintain overall health. Ideally, the management of osteogenesis imperfecta is handled by a team of specialist doctors, including orthopedic and medical rehabilitation. Supportive therapy is individualized, depending on the degree of damage that occurs and the age of the patient with osteogenesis imperfecta. Moral support is also given to parents and families of sufferers so that these parents feel comfortable or not frustrated in caring for their babies or children who suffer from osteogenesis imperfecta, especially parents with babies with type II osteogenesis imperfecta.[12]

The goal of orthopedic management is to treat osteogenesis imperfecta with fractures and prevent or correct bone deformity. Bracing, splinting, and orthotic actions are one of orthopedic management. The surgical procedure performed in general is rodding, which is placing a metal material in the long bones, which is used to strengthen the bones so that the risk of fracture is minimal. Immobilization measures can be carried out with lightweight materials, which aim to avoid further fractures due to the material used. In general, people with osteogenesis imperfecta have the same speed of bone recovery as normal bone.[13]

Pharmacological management in the form of growth hormone treatment, intravenous or oral bisphosphonate drugs, and gene therapy.[14] Bisphosphonate is a synthetic analogue of pyrophosphate, which inhibits osteoclast bone resorption by binding to hydroxyapatite in bone, thereby increasing bone mineralization and strengthening bones. Bisphosphonates increase bone density by increasing the growth of the cortex and trabeculae of bone.[15] However, bisphosphonate therapy is not the main treatment of osteogenesis imperfecta. The therapy only increases the quantity of bone without correcting genetic effects. Zoledronic acid is one of the bisphosphonates that is often used in osteogenesis imperfecta. The dose used is based on age and is given intravenously (IV).[10] BMD has to do once every year to evaluate the zoledronic acid treatment.

Medical rehabilitation has an important role in the supportive therapy of OI patients. With rehabilitation exercises, the patient's muscles, ligaments, and bones are trained to become stronger and better prepared to carry out daily activities. Assistive devices that are often found in medical rehabilitation are often needed. This patient was given special footwear due to a lower limb-length discrepancy.

Patients with osteogenesis imperfecta who are prone to trauma and require long-term immobilization due to fractures often experience vitamin D and calcium insufficiency. Therefore, it is necessary to supplement with 400-800 IU of vitamin D and 500-1000 mg of calcium as prophylaxis, although it does not improve osteogenesis imperfecta itself. Daily supplementation of

1200 IU of vitamin D and 250 mg of calcium when body weight is <15 kg, 500 mg of calcium if body weight is >15 kg. The dose of vitamin D is then periodically adjusted to avoid hypercalciuria and nephrocalcinosis.[16]

4. Conclusion

Osteogenesis imperfecta is a complex hereditary disease characterized by a striking clinical variability necessitating a logical classification system. It is caused by recessive or dominant variants of mutation in different genes, which encode proteins involved in collagen type I biosynthesis and require multidisciplinary management and further research of therapeutic approaches such as bisphosphonates.

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PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7