Brittle bone brothers: osteogenesis imperfecta conventional serial case

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ABSTRACT

**Background:** Osteogenesis Imperfecta (OI) is a heredity connective tissue disorder due to COL1A1/2 gene mutation, causing a defect in encoding proteins to metabolize collagen. One of OI’s manifestations to musculoskeletal is bone incompetence, hence the name Brittle bone disease. We report three cases of OI type IV in adults with pathognomonic radiology findings.  

**Case Presentation:** In Case 1, a 40-year-old Indonesian male came to the hospital with small stature and unsuited with his age. Conventional radiology examination found OI on all four extremities, anterior dislocation of left shoulder, and old fracture with an acute angle in the left radial shaft. In Case 2, a 41-year-old Indonesian male came to the hospital with short stature, causing limitation to his activities, and he confessed always to be shorter than people his age. Radiology evaluation suggests an OI in bilateral superior and inferior extremities, old fractures in the right humeral shaft also the left clavicle, acute angles right radius-ulna shaft, and osteoporosis in all visualized bones. In addition, in Case 3, a 42-year-old Indonesian male came to the hospital with short stature and pain within his bones, causing limitation to his activity. Conventional radiology imaging shows bilateral superior and inferior extremities, old fracture in the medial third of the left humerus and bilateral femur, acute-angled bilateral antebrachial-femur-cruris, and osteoporosis.  

**Conclusion:** Based on OI categorization, only type I and IV can live to adulthood, and the same type of OI can be found in siblings. Conventional radiology imaging provides a great help in diagnosing OI.  

**Keywords:** Osteogenesis Imperfecta, Heredity Disorder, Conventional Radiology, Brittle Bones, Skeletal Deformity.  


INTRODUCTION

Osteogenesis imperfecta (OI) comprises a heterogeneous group of diseases characterized by susceptibility to bone fractures with variable severity and, in most cases, with presumed or proven defects in collagen type I biosynthesis.¹ The OI or Brittle bone disease is a congenital disorder caused by a mutation to COL1A1 and COL1A2 genes, which are essential to collagen metabolism, causing a disturbance in all connective tissues composed of type I collagen, causing fragility of skeletal bones, multiple fractures and in the end early osteoporosis to the patients.²

Incidence of overall OI reaches 1:20,000 births, OI type I reached 2.35 – 4.7:100,000 births, OI type II reached 1.1.4:100,000 births, incidence of OI type III and IV are still unknown, but the most widely found is OI type I.³ Although about 85–90% of cases are caused by structural or quantitative mutations in the collagen genes themselves, the disorder is now more fully understood as a predominantly collagen-related disorder.⁴,⁵

Forlino A and Marini JC in 2016 described nineteen types of OI, including five main categories based on genetically metabolic function defects.³ However, the initial diagnosis is largely based on clinical and radiographic findings.³ Based on those mentioned above, this case study aims to report three brothers with OI type IV and these brothers are the only adults with OI in Sanglah General Hospital, Bali, Indonesia.

CASE REPORT

**Case 1**

A 40-year-old Indonesian male came to the hospital with small stature and unsuited with his age. The patient admitted having various fractures while he was young without any trauma or accidents. On physical examination, we found over-bending to be upper and lower extremities, and the patient had normal sclera colorization also normal teeth. Radiological conventional imaging on upper and lower extremities revealed generalized bowing to the radial, ulnar, metacarpal bones, femur, tibia, and fibula. There are also acute-angled with multiple non-union fractures in bilateral humeral bones, old fracture with an acute angle on the left radius, osteoporosis in all visualized bones. There is also anterior dislocation of the left humeral head. Chest X-ray showed
to his activities, and he confessed always to be shorter than people his age. The patient said to have unexplained pain throughout his extremities accompanied by a broken sound. Physical examination showed generalized bending deformation to all extremities, and he has normal sclera with yellowish-brown opalescent discoloration of anterior teeth and some missing ones. Conventional radiology imaging showed bowing in bilateral femur, tibia, fibula, and the left humerus also acute-angled bilateral antebrachial-femur-cruris and osteoporosis.

**Case 2**

A 41-year-old Indonesian male came to the hospital in short stature, causing limitation to his activities, and he confessed always to be shorter than people his age. The patient said to have unexplained pain throughout his extremities accompanied by a broken sound. Physical examination showed generalized bending deformation to all extremities, and he has normal sclera with yellowish-brown opalescent discoloration of anterior teeth and some missing ones. Conventional radiology imaging showed bowing in bilateral femur, tibia, fibula, and the left humerus also acute-angled on bilateral radius and ulnar shaft. A few missing bones in the right humeral shaft suspicion caused by old fracture also enlarged the distal metaphysis of bilateral distal femur, tibia, and fibula. Cardiopulmonary abnormalities were absent, but overall bones are severely porotic, and also, there was an old fracture to the left clavicle with bowing to his ribcage. Radiographic images are in Figure 2.

**Case 3**

A 42-year-old Indonesian male came to the hospital with short stature and pain within his bones, causing limitation to his activity. Physical examination showed bent bilateral superior-inferior extremities with normal sclera and teeth. Further conventional radiology imaging showed bowing deformities to all long bones, missing bone parts on the medial third of the left humerus and left femur, enlarged metaphysis on all long bones, acute angles in bilateral antebrachial, bilateral femur, and cruris, old fracture in the right femur and severely porotic bones. Chest conventional radiology showed bent ribs, deformed left clavicle and cardiopulmonary abnormalities were absent. Radiographic images are in Figure 3.

**DISCUSSION**

OI is a hereditary connective tissue disorder due to COL1A1/2 mutation causing gene defect encoding proteins to metabolize collagen. OI’s skeletal manifestation mainly causing bone incompetence, vulnerable to fractures, deformed, and joint laxity. Therefore bones are fragile, hence the name of Brittle Bone Disease. Forlino and Marini in 2016 described nineteen types of OI with five main categories based on genetically metabolic function defects, such as defects in collagen synthesis, structure or processing (Group A- type I-IV, XIII), defects in collagen modification (Group B-VII-IX, XIV), defects in collagen folding and cross-linking (group C- type X-XI), defects in bone mineralization (group D- type V-VI) and defects in osteoblast development with collagen insufficiency (group E-type XII, XV-XVI). Current therapy for OI is integrative, pain management, muscle rehab for regaining strength and range of movement, restore mobility to increase the quality of life, and a regular check-up for dentition and hearing. Bisphophonate treatment with cyclic intravenous Pamidronate given in infancy proved to help increase bone density and reduce fractures.

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In these brothers’ cases, their ages range from 40-42 years old; they have a small stature, normal sclera, two patients have normal teeth, and one with Dentinogenesis Imperfecta (DI). These brothers generally have the same type of OI, which is OI type IV. Still, different subtypes, IV A without DI and IV B with DI. Genetically categorized as group A by Forlino and Marini, type IV OI resulted
in COL1A 1 or 2 mutation. Genetic workup must be done to determine which one. Unfortunately, genetic workup was not administered to all patients.

Type IV OI categorized as group A in Forlino and Marini classification is caused by collagen deficiency creating structural inadequacy. Glycine substitutions in the helical domain are the most common problem, delaying helical folding and prolonging time to modify enzymes. Another mutation common for OI is the impaired chain of procollagen C-propeptide. Inadequate collagen structurally can manipulate intracellular metabolism and matrix architecture rather than a deficiency in collagen quantity. General radiographic findings mostly consist of osteopenia, deformities, and fractures. Common findings to lower extremities include anterior or lateral bowing of the femur, anterior bowing of the tibia, protruded acetabulum, and ‘Shepherd’s crook’ deformities in the proximal femur. ‘Popcorn’ appearance in the metaphysis, multiple areas, or radiolucent scalloping with thick rims can be seen in some patients with OI. Specific findings of the spine include compressed vertebrae between cartilaginous disc space, called codfish vertebrae. Abnormalities were found in long bones and in the skull, which is caused by excessive bone malleability and plasticity. The more common findings to the skull are multiple wormian bones, a physiological finding in the skull, but considered abnormal if there were more than ten found and usually present in patients with severe OI.

Diagnosis of OI in childhood made solely with conventional skeletal radiographic images, simple yet effective. An optimal method to determine quantitative osteopenia is using Dual-Energy X-ray Absorptiometry (DEXA) and Bone Mineral Density (BMD) score will reveal if there is only osteopenia or already in osteoporosis state. Another method to diagnose OI in children is with DNA analysis with an examination of cultured fibroblast. This method showed a decreased quantity of cultured fibroblast in children with OI than healthy children. It also showed abnormality of type 1 procollagen molecules or mutation to COL1A1 or COL1A2 genes that encrypt type 1 procollagen chains. Bone histomorphometry examined in OI type I-IV (collagen defect group) showed low bone volume and trabecular quantity with high replacement kinetic rates. If more than one family member has this disease, the clinician should explore the OI gene panel for a better therapy plan.

CONCLUSION
OI is a rare genetic disorder to the musculoskeletal system caused by mutations to type 1 collagen in connective tissues. OI are classified based on skeletal structure, sclera colorization, dentinogenesis imperfecta, and functional metabolic defect genetically. OI type I and IV can live until adults; the same type of OI can also be found in siblings. Skeletal conventional radiographic imaging can solely make the diagnosis of OI.

CONFLICT OF INTEREST
The authors declare that there is no competing interest regarding the manuscript.

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AUTHOR CONTRIBUTION
All of the authors equally contribute to the study from the conceptual framework until reporting the case study results through publication.

REFERENCES