

# Osteogenesis Imperfecta Congenita

—Five cases and review of the literature—

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## ABSTRACT

Recently, five cases of osteogenesis imperfecta have been observed at Severance Hospital, Yonsei University. Two newborn females, two female children (one year and eight months, five years) and a male child (five years and four months) were typical examples with multiple bone fractures, blue sclerae, and deformity of extremities. The mother of case 3 has also had blue sclera but no history of bone fracture. In case 1, a chromosome study was done because the infant had a short neck, low set ears and a high arched palate besides typical signs of osteogenesis imperfecta of which result was found as normal karyotype. In case 3, the patient also presented the rachitic changes of the long bones and ribs and exhibited congenital agenesis of the right kidney. In case 4, the blue sclera was questionable.

Three cases only have been reported prior to this study in Korea. We are presenting another five cases of osteogenesis imperfecta congenita, its pathology and a brief review of the literature.

## INTRODUCTION

Osteogenesis imperfecta congenita or Fragilitas ossium is differentiated from osteogenesis imperfecta tarda (or Lobstein's disease) but both seems to be transmitted by a Mendelian dominant trait. The earliest report on osteogenesis imperfecta congenita was made by Vrolik in 1849, but the tarda form was reported earlier by Lobstein in 1835 (Navani and Sarzin, 1967).

According to the review by Chawla and Madan (1963), only 120 cases have reported until 1963 in the world literature.

Incidence of the disease (variable by each reporter) is one in 25,000 deliveries in India (Sarma, 1960), one in 21,000 deliveries by Freda et al (1961), one in 13,052 deliveries by Navani and Sarzin (1967).

Potter (1962) has described the cardinal signs of this disease as easy bone fracture, blue sclera and osteosclerosis. But it was recently found by Stelling (1967) that the basic pathology originated from a generalized disorder of the connective tissue of bone, tooth, sclera, ligament, tendon and skin.

There are only three case reports of osteogenesis imperfecta congenita up to the present

investigation in Korea (Choi and Yoon, 1959; Park and Song, 1963; Lim et al, 1967).

But recently we have found another five cases at Severance Hospital, Yonsei University, Seoul, Korea.

#### Case 1.

A newborn female was delivered by a 30 year old multigravida Korean woman of 42 weeks gestation by normal spontaneous vaginal delivery. Brith weight was 3.1 kg. After birth short extremities, membranous skull and severe crying at bathing and diapper changing were described.

Family History: Parents and two siblings are healthy and none have anomalies. Among her relatives no one has a history of fracture or blue sclera (including grand parents and her cousin).

Physical Examination: The four extremities were curiously short and she cried excessively on palpation of her extremities and head. Her nutrition was fair and measurments were as follows: head circumference 38.2 cm., a little bit larger than normal, chest circumference 32.5 cm. The extremities were short in comparison to her trunk and her digits were also

short compared to the palm, which looked out of proportion (Fig.1). No anomaly was noticed in the face but her skull was so sofe and membranous that it was easy to make a digital marking by light pressure. Both sclerae were blue in hue and both ears were set in low position and her palate was highly arched. Her neck was short. Both lungs were clear and no murmur was audible by auscultation. Adomen was negative. The range of motion at each joint was wider than usual and multiple flactures were easily detectable by palpation at the upper portion of the tibia (Fig. 4). The neurological



Fig. 1. Genesal features at birth of case 1.



Fig. 2. Skull X-ray (A-P) shows widening of the biparietal diameter with thin cranial table and multiple wormian bone giving appearance of mosaic pattern. (Case 1)

examination including Moro reflex was within normal limits.

Laboratory; VDRL was negative in both mother and infant, and complete blood count revealed the following; Hb, 16.2 gm%, white cell count. 19,800/mm<sup>3</sup>, neuophil 74%, lymphocyte 21%, monocyte 4% and Hct. 56%. Serum calcium was 8.8 mg%, phosphorus, 4.7 mg%, alkaline phosphatase; 3.2BU, which were within

normal limit. The urine examination showed also normal.

X-ray Study; Skull X-ray showed widening of bilateral diameter with thin cranial table and multiple wormian bones giving appearance of mosaic pattern (Fig. 2). Chest X-ray including the upper extremities and upper portion of the abdomen showed slender ribs, bowed extremities and fractures with callus formation of the right radius and left ulna (Fig. 3). Another film showed multiple fractures with callus formation of the lower extremities which resulted in deformities (Fig. 4).

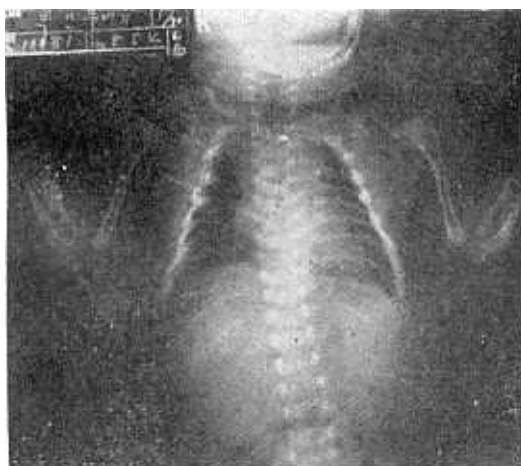


Fig. 3. Chest including upper extremities shows slender ribs, bowing of the extremities and fracture with callus formation at the right radius and left ulna. (Case 1)

Chromosome study; As she has a bony defect with multiple anomalies, already mentioned, chromosome study was done. Blood was drawn from femoral vein aseptically and lymphocytes were cultured by the Moorhead technique (1960). We analyzed 50 cells with chromosomes in the stage of metaphase. Those were normal in number and form both in autosome and sex chromosome; the number was 46(XX) (Fig. 5 and 6). Buccal smear study showed a normal

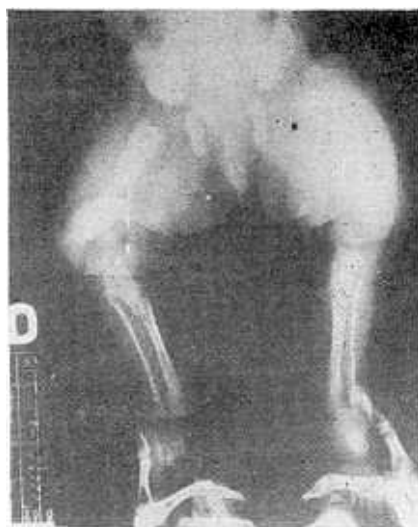


Fig. 4. Lower extremities show multiple fractures with callus formation and reveals marked deformity at the both femur due to fracture. (Case 1)

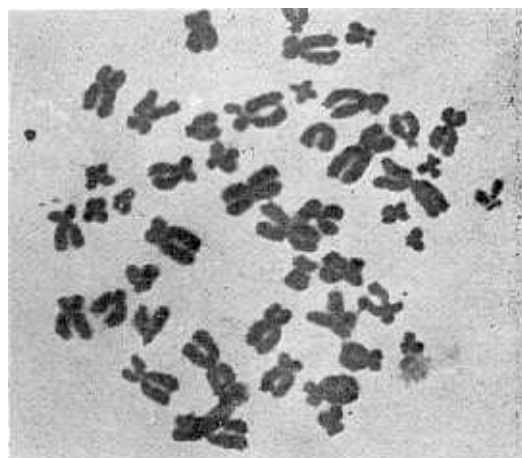


Fig. 5. Chromosome spread in metaphase of Case 1.

Barr body.

Hospital course; She was fed glucose water at 12 hours after birth. Her sucking power improved gradually and at 72 hours, she was able to breast feed. As her general condition improved, her parents took her home voluntarily on the 4th day after birth.

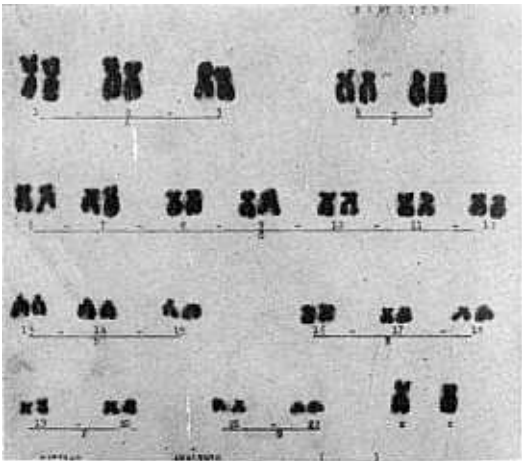


Fig. 6. Karyotype of case 1 showing 46(XX).

Case 2.

This is a Korean female infant who was born at a hospital at 41 weeks of gestation from a multiparous mother aged 37 year, and her birth weight was 2.6kg. Mother, father (41 year old) and three siblings were healthy. None of them have blue sclera or history of fracture. According to her mother's statment, mental and physical growth and development were normal in her other sons.

Physical Examination. It was easy to notice that the legs were unusual at a glance; her left leg was completely flexed and abducted. The range of articular movement at the hip joint was so wide that it seemed it had no limitation of motion. She cried every time at diaper changing and her skull was soft enough to make a digital marking by light pressure(Fig. 7). The sclera was blue in color and there was no anomaly in the trunk. The upper extremity was normal in appearance and without fracture.

Laboratory; Hb was 18.5 gm%; white cell count; 34,400/mm<sup>3</sup>, neutrophil 63%, lymphocyte



Fig. 7. General features at birth of Case 2.

34%, and monocyte 1%; Hct, 49%. Serum calcium was 9.2 mg%, which was within normal limit.

X-ray study; Skull X-ray showed thin and porotic changes with the appearance of mosaic pattern. Biparietal diameter was increased (Fig. 8). X-ray of lower extremities showed bowing



Fig. 8. Skull is thin and porotic with appearance of mosaic pattern. Biparietal diameter is increased. (Case 2)

and deformity. The left leg was fractured and callus formation was noticed at both femurs. The epiphyses of long bones were large, and both fibulas were slender and bowed (Fig. 9).



Fig. 9. Both lower extremities are bowed and deformed. Fracture with callus formation is noted of both femurs. Epiphyses of the long bones are large. Both fibulae are slender and bowed. (Case 2)

Hospital course; Her general condition improved gradually but her parents took her to their home against advice on the third day.

No follow-up is available.

### Case 3.

This is a Korean boy, age 5 years and 4 months, who was admitted to this hospital due to retardation of growth and disturbance of standing and walking.

Past history; He was born by normal spontaneous vaginal delivery from an elderly multiparous mother.

No specific history related to his complaint was obtainable in an antenatal or birth history. At birth, the mother said, he was a normal infant and he was breast fed.

He has never consulted a physician about his developmental retardation as his parents thought it might be an uncontrollable congenital disease.

He had an episode of fracture of his left humerus and right femur by light trauma at the age of three.

Family history; Parents and five siblings were healthy and no one had an episode of fracture. His mother had blue sclerae. And no one had mental or physical retardation.

Physical Examination; This boy was poorly developed but well nourished and clear mentally. The weight; 12 kg, length; 85 cm, chest circumference; 52cm and head circumference; 50 cm, which were compatible to the 50 percentile of standard growth of two year and six months of Korean children. Head was asymmetric and posterior aspect of his head protruded laterally. His face was normal looking. He could control his neck and grasping power was strong enough.

Both sclerae were blue in color and the fundi were normal by fundoscopic examination. He had no hearing disturbance and he had 22 teeth which was considered normal for his age. The chest wall protruded forward like a pigeon chest and rachitic rosary was noticed at the costochondral junctions. Both lungs were clear and no murmur was audible on auscultation. Abdomen was normal. Spinal column was kyphotic. The left arm curved medially, which was thought to be an unsuccessful union after fracture.

Laboratory; Blood cell counts and biochemical studies were done; Hb; 11.5 gm%, white cell count; 7,600/mm<sup>3</sup>(neutrophil 37%, lymphocyte 59%, monocyte 2%) serum protein; 7.42 mg% (albumin; 4.92 gm%, globulin; 2.47 gm%), serum calcium; 8.1 mg%, P; 3.6 mg%, NPN; 31 mg%, BUN; 14mg g% which were within normal limits. Alkaline phosphatase was 24~28 BU which was done several times. Stool examination, urine examination, Mantoux test, VDRL and Kahn test were negative. The psychiatrist was consulted for his mental development and they found his mental state was compatible to

that of an imbecile.

**X-ray Studies:** Demineralization was found of all bones and the skull table was thin and the spinal column was bowed forward due to compression fractures. Ulna and radius showed fractures with bowing, callus formation, and periosteal elevation. The distal end of the radius and the ulna revealed widening with cupping deformities.

Decreased and increased radioopaque zones were noted at the distal metaphysis and their ends showed brush ending pattern. The cartilage zone of the radius was also widened. These signs were thought to be typical of rickets with rachitic rosary. The rachitic pattern seen at the metaphyses was improved on another film taken two months later after discharge (Fig. 10 and 11).

**Hospital course;** This patient has impressed us that he had osteogenesis imperfecta congenita, but we kept on studying him for four weeks

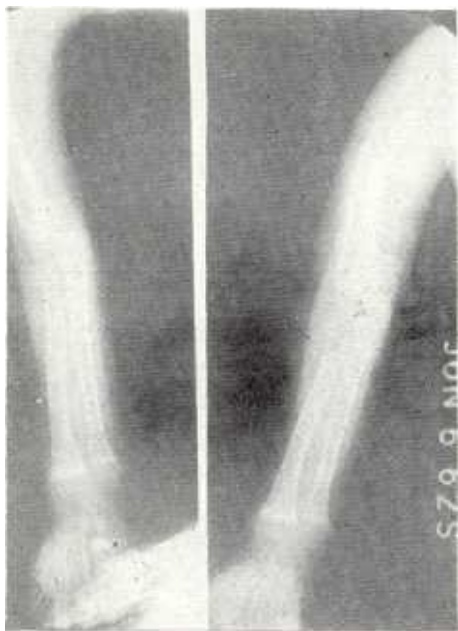


Fig. 10. Upper extremities show generalized osteoporosis and fracture with bowing at the right ulna showing callus formation and periosteal elevation. (Case 3)

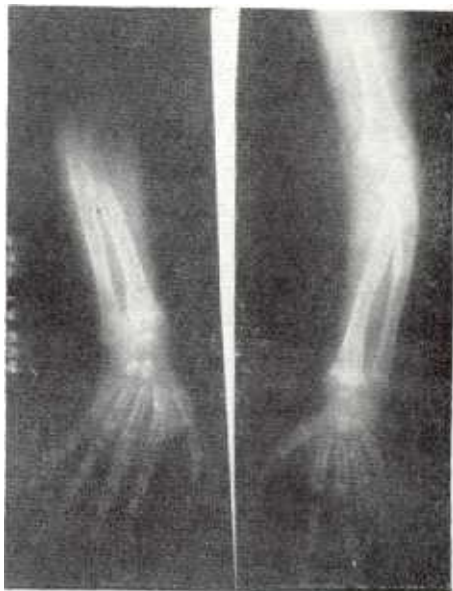


Fig. 11. Distal radius and ulna reveal widening with cupping deformity. Decreased and increased zone are noted at the distal metaphyses. Cartilage zone of radius is widened. (Case 3)

as he might have had this disease combined with renal rickets, hyperparathyroidism or Fanconi's syndrome. But we ruled them out by various chemical and radiological studies. It was also known that he had congenital agenesis of the right kidney by various radiological studies. He had been on vitamin A and D without improvement clinically and radiologically during the present admission. He was discharged on the 46th hospital day.

#### Case 4.

This is Korean female orphan, aged approximately 1 year and 8 months because her family and past histories were not certain. She has admitted to our hospital for remedy for fracture.

According to her care taker's information, she had a history of easy fracturability.

**Physical Examination;** She seemed to be retarded in growth and development but it was hard

to evaluate precisely because her exact age was not known.

The anterior fontanel was widened. Both humeri were bowed which was thought due to old fracture and healing. Swelling and fracture were noticed of the left thigh. The sclerae were not frankly blue in color.

Laboratory; Hb; 10.6gm%, white cell count; 24,500/mm<sup>3</sup> (neutrophile 46%, lymphocyte 54%), serum calcium; 8.9mg%, phosphorus; 4.8mg%, alkaline phosphatase; 3.82 BU and other biochemical tests were within normal limit.

X-ray study; Bone X-ray showed osteoporotic changes of the whole skeletal system due to demineralization. On skull X-ray, widened sutures were noted. Marked bowing and narrowing were found on the long bones. Multiple fractures and callus formation were found of the humerus and femur.

Hospital course; Even though she had no blue sclerae, it was certain that she had been suffering from osteogenesis imperfecta by radiologic study of her skeletal system. She received treatment only for her fractured femur, and she was discharged.

#### Case 5.

This is also a Korean female orphan, age of five years. She was admitted to our hospital due to anomalies of her hands and feet and inability to walk.

She initially visited the orthopedic surgical department for surgical correction of her skeletal deformities.

As she was an orphan, it was impossible to know her past and family histories as well as her exact age.

It was only known that she had abnormal hands and feet when she was brought to the orphanage, when she was a baby.

Physical Examination; Her physical develop-

ment was retarded for her age but her head was the size of an adult's.

She had blue sclerae and limped because of her curiously deformed feet. Both her thumbs were curved medially. She had no other external anomaly.

Laboratory; Blood cell count, urine examination, stool examination, and biochemical studies were within normal limit.

X-ray study; The long bones of the upper and lower extremities were markedly bowed, slender and showed generalized demineralization. Knee joints were subluxated and the pelvis was flat and narrow. Both flat femoral heads were subluxated from the acetabula. Another film of the spine and ribs showed normal bony configuration and the skull was unusually big for her age and showed osteoporotic changes, which was thought due to decalcification.

Hospital course; As her symptoms were slight and she did not need care from Pediatrics, we retransferred her to the Orthopedic surgery for surgical correction.

## DISCUSSION

Osteogenesis imperfecta is not a rare disease among the congenital connective tissue disorders (Choi and Yoon, 1959) and the characteristic symptom of this disease is easy bone fracture. For this reason, Rubin (Stelling, 1967) thought it to be due to an intrinsic dysplasia of the skeletal system. McKusick thought that this disease was a generalized connective tissue disorder and resulted in thin and blue sclera, loose articulation, underdevelopment of teeth, deafness, fragility of bones, that is seldom painless, and resulted in a short and contracted stature (Stelling, 1967).

This disease can occur in all races (Choi and Yoon, 1959), with no sex difference (Ginsberg, 1962).



In congenital form, family history is seldom uncertain compared to that of osteogenesis imperfecta tarda (Nelson, 1964), in which blue sclera is noticed in all the family members and deafness in one fourth of all the cases (Nelson, 1964). But in those cases we have observed, we noted no blue sclera or previous fractures in the family members except for the third case. Among the three cases, reported in Korea, only one patient, that mentioned by Choi (1959), had a positive family history. Gilchrist and Shore (1967) have reported two sisters in a family both suffering from lymphocytic leukemia associated with osteogenesis imperfecta. In chromosome study of those patients no abnormal chromosome in the karyotype was found.

Although their chromosomes were normal, both of them had familial lymphocytic leukemia, they believed it might be related to an underlying genetic factor.

In our experience, we found normal chromosomes in the first case,

Fractures and various stages of callus formation are some times noticed in the intrauterine period by radiologic evaluation especially in a severe case (Potter, 1962). Considering the mechanism of the frequent episodes of bony fracture, it is known that osteoblastic activity may be defective and results in deficient bony development and slender bone are apparent in the X-ray of the patient (Potter, 1962, and Choi and Yoon, 1959).

Chowers et al (1962) made biochemical examinations on six patients and their families such as blood urea, glucose, creatinine, uric acid, aminoacid, electrolytes (Na, Ca, Cl, P.), alkaline phosphatase, and urine examinations and electrophoresis of serum protein and liver function tests. They found aminoaciduria in all patients even though their serum aminoacid levels were normal, and the creatinine levels in the blood

were decreased.

Other tests were within normal limit. They recommended testing aminoacids in urine of patients suspected of having osteogenesis imperfecta, especially who had blue sclera, because they found aminoaciduria in the family members who only had blue sclera without symptoms. Unfortunately we could not study urine aminoacids in our patients and their families.

In the third case, the elevated alkaline phosphatase level may be explained by the fact that patient had rickets. Other patients had normal alkaline phosphatase level. Appearance of bone of the patients usually depended to chance to examine any members of the family except their parents. Some of parents were not willing to tell the true family history and it might not be an accurate report.

Because the third patient had such mild symptoms we suspected this was osteogenesis imperfecta tarda, but X-ray evidence of the widened ends of long bones fit the congenital form and because the symptoms were so mild it is probably one of reasons why he was still alive.

In the severe congenital form, patients may die just after birth or be still born. In some mild condition, the patient may survive (Nelson, 1964 and Stelling, 1967). But it can not be said that this disease has a good prognosis as most patients are left crippled (Nelson, 1964).

Fortunately this disease is not a common one through the whole world.

In Korea only three cases previously have been reported, we hereby add another five cases from our experience.

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