

CURRENT APPROACH TO OSTEOGENESIS IMPERFECTA: CASE STUDIES OF A MOTHER AND SON WITH OSTEOGENESIS IMPERFECTA**Tuba Tülay KOCA^{1*}, Tolga Bağlan², Ülkü Demir³, Gülbahar Saraç⁴, Ahmet Uğur Boz⁵**¹State Hospital, Physical Medicine and Rehabilitation, Malatya, TURKEY.²Numune Training and Research Hospital, Cytopathology Clinic, Ankara, TURKEY.³State Hospital, Ophthalmology Clinic, Malatya, TURKEY.⁴State Hospital, Dermatology Clinic, Malatya, TURKEY.⁵State Hospital, Cardiology Clinic, Malatya, TURKEY.***Correspondence for Author: Dr. Tuba Tülay KOCA**

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ABSTRACT

Osteogenesis imperfecta (OI) is a genetic disorder that causes bone fragility and fractures in children and adults. OI type 1 is frequently associated with the mutations in collagen genes. It affects many tissues and organs which contain type 1 collagen. OI is classified clinically and radiologically into four major groups based on phenotype and inheritance pattern; however, rare subgroups with unique features have also been described in the recent years. A 38-year-old female patient was admitted to the clinic with a complaint of back pain. Her medical history comprised minor trauma and frequent fractures (shoulder and ankle). The patient was fair-skinned, and her physical examination revealed an increase in thoracic kyphosis, blue sclera, and joint hyperextensibility. The total vertebra T score and Z score were -4.0, and -3.5, respectively, in the dual-energy x-ray absorptiometry examination. The patient was a first-degree relative of her husband. The medical history of her 16-year-old son showed seven fractures (both shoulders, ankle, right wrist, and fingers of the right hand), which were caused by minor traumas. His physical examination findings included bluish sclera, trigonocephaly, triangular face, pectus carinatum, and joint hyperextensibility. Systemic involvement was evaluated in both the patients. The different histories and phenotypic features of the mother and her son with OI plays an important role in understanding the nature of the disease and current approaches.

KEYWORDS: Osteogenesis imperfecta, osteoporosis, pathologic fracture.**INTRODUCTION**

Osteogenesis imperfecta (OI) is a rare genetic disorder that causes bone fragility and fractures in children and adults. OI type 1 is frequently associated with mutations in the collagen genes; however, many other genes secondarily related with the production of type 1 collagen have also been identified in this disease.^[1]

OI is also termed as Lobstein syndrome, brittle bone disease, or blue sclera syndrome². The oldest cases of OI were the mummified infant skeletons found in ancient Egypt. Lobstein coined the term osteogenesis imperfecta and was one of the first to accurately understand the etiology of OI in 1835.^[1-3]

OI is one of the most frequent skeletal dysplasia and a generalized connective tissue disorder. It may present with one or more findings of blue sclera, triangular-shaped face, craniofacial defects, hair loss, defective dental structure, barrel chest, scoliosis, extremity deformities, fractures, joint laxity, growth retardation, and so forth.^[1-3] This study reviewed cases of a mother

and her son with OI who presented with different clinical symptoms.

Case I

A 38-year-old female patient in the premenopausal period was admitted to the physical medicine and rehabilitation clinic with the complaint of back pain.

The patient had a medical history of single ankle fracture during her childhood, right shoulder fracture in her young adulthood, and left shoulder fracture after lifting a chair 5 years ago. The patient had regular menstruation cycles and no known disease. The patient was a first-degree relative of her husband (cousins). She had two daughters (21 and 18 years old) and one son (16 years old). Neither her husband nor her daughters had any complaints.

The only findings in the physical examination of the patient's 18-year-old daughter were hyperelasticity of the joints and mitral valve prolapses on electrocardiography (ECG). The patient was fair-skinned (Fig. 1).

Her physical findings revealed blue sclera, hyperextensibility in all joints and an increase in thoracic kyphosis. The laboratory test results were as follows; 25'OH vitamin D is 3.37 ng/mL (normal range: 10–44) parathyroid hormone (PTH) is 70.43 pg/mL (normal range: 15–65). The other laboratory parameters were within normal ranges. Sporadic loss in the height of thoracic and lumbar vertebrae was observed on conventional spinal radiographs (Fig. 2).

The dual-energy x-ray absorptiometry examination (DXA) revealed the T score as -4.0 and Z score as -3.5 for L1–L4 levels; Z score and T score were -0.9 and -1.7 , respectively, for femur and neck. Treatment was started with active vitamin D metabolite and weekly oral bisphosphonate. Strengthening exercise of back extensor muscles and dietary regulation were recommended for the patient.

The patient was referred to the ophthalmology, otorhinolaryngology (hearing test was normal), cardiology (electrocardiography and echocardiography were normal), and pulmonary medicine clinics for consultation.

Case II

The medical history of the 16-year-old male patient comprised seven fractures in the ankle, right wrist, and both shoulder joints; the most recent one was in the second finger of the right hand caused by compression of the hand between the desks. His physical examination revealed blue sclera, triangular-shaped face, trigonocephaly, pectus carinatum, and increased prominence of both acromions (Figs. 3 and 4). The laboratory test results were as follows; 25'OH vitamin D is 5.62 ng/mL (normal range 10–44) phosphorus is 5.3 mg/dL (normal range is 2.3–4.7) and alkaline phosphatase is 414 U/L (normal range is 40–100). The other laboratory parameters were within normal ranges. A minimally displaced fracture associated with the distal growth plate of the second metacarpal bone was observed on the conventional radiograph of the right hand. A short arm splint was made for the right hand of the patient. Treatment with active vitamin D metabolite was started. Dietary regulations against osteoporosis and a joint protector were recommended for the patient. He was referred to the ophthalmology, pulmonary medicine, and otorhinolaryngology clinics for consultation regarding systemic involvement and complications.

Figure 1: The 38-year-old fair-skinned patient with blue sclera.

Figure 2: Sporadic loss in height is observed on the conventional lateral radiographs of thoracic and lumbar vertebrae.

Figure 3: Dysmorphic findings of the 16-year-old male patient: trigonocephaly and triangular-shaped face.

Figure 4: Pectus carinatum is observed on the lateral view of the chest.



DISCUSSION

OI is a group of clinically and genetically heterogeneous connective tissue disorders. The incidence of the forms diagnosed at birth is 1/15–20,000. The main features of OI are fractures caused by minimal traumas, bone deformities, and bone fragility due to susceptibility to growth retardation.^[1-3] Fractures in both the cases occurred after performing mildly compelling activities such as lifting a chair.

Previously, the disease was considered to be an autosomal dominant bone dysplasia caused by a defect in type 1 collagen. However, recognition of the recessive genes over the past decade has supported the pathophysiological theory involving collagen predominantly and contributed to the understanding of the nature of the disease.^[3] Autosomal dominant external transition is supported by the fact that the daughters had no complaints whereas the son had clinical and phenotypic findings. In 1979, Sillence et al. developed a classification system based on the clinical features and severity of the disease to determine the subtypes of OI. They classified OI into four subgroups: type 1 is the most common form of OI that has a mild clinical course with blue sclera; type 2 is the perinatal lethal form of OI; type 3 has a serious clinical course with progressive deformities and a normal sclera; and type 4 has a moderate clinical course with normal sclera.^[3]

Approximately 90% of the patients with OI have a dominant inheritance pattern and heterozygous or sporadic mutations in *COL1A1* and *COL1A2* genes. Different metabolic pathways associated with collagen might be affected in patients with OI, including synthesis, post-translational modification, folding and cross-binding pathways, mineralization, and osteoblast differentiation. Very rare subtypes of OI have been discovered over the past decade; they have an autosomal recessive inheritance pattern and occur due to a defect in the proteins involved in the post-translational modification and folding of collagen. Additionally, idiopathic cases have been reported. Patients with OI may have a wide range of clinical and genetic features.^[3,4] The 38-year-old patient had no significant complaint when she came to the clinic, except a couple of fractures as evident in her medical history. The patient was evaluated for OI type 1 according to the Sillence classification which is frequently seen form with blue sclera and mild course. The 16-year-old male patient with a medical history of frequent fractures, blue sclera, triangular-shaped face, trigonocephaly, and pectus carinatum was evaluated for a different clinical type of OI that is not consistent with any of the aforementioned four forms. Different genetic transition patterns are indicated by the fact that the daughters had no complaints whereas the son had multiple fractures due to minor compelling activities in his medical history. Furthermore, OI is seen with equal frequency in both males and females, and follows a similar course.

Fractures are common in childhood. However, they can be the symptoms of bone fragility as the primary or secondary cause of fractures. The main topics of the discussion are determination of the whether these children need an advanced research or not and which of them needs. A child who has more fractures without any association with mild or moderate trauma should be sent first for history examination (family history), physical examination, spinal radiography, and DXA of the skeletal system.^[3-5]

No advanced examination was performed for the patient, although his medical history showed seven fractures. Thanatophoric dysplasia according to the age of the child and severity of the disease, achondrogenesis type 1, campomelic dysplasia, hypophosphatasia, and child abuse can be considered in the differential diagnosis of OI.

The disease affects both endochondral and intramembranous ossification.^[6] Abnormalities of the head and face shape can be seen in OI due to a craniofacial defect during the growth period. Trigonocephaly and triangular-shaped face were observed in the male patient. The results of the intelligence test were consistent with the age of the patient.

Type 1 collagen is the major component of connective tissue and it constitutes major proportions of many organs. Although the bone phenotypes are well identified in OI, the effect of reduced collagen on other organs is not well known.^[2] Multiple secondary features might be seen in the clinical course of OI such as dentinogenesis imperfecta, hearing loss, neurological defects (basilar invagination), and cardiopulmonary complications (the major cause of death in OI).^[1-3] These patients may visit a doctor's office with the extra-skeletal complaints of organs.

Pectus carinatum is a progressive congenital abnormality of the anterior chest wall. The name was given based on its morphological similarity to the keel of the ancient Roman ships (carina). It is associated with different diseases such as Marfan syndrome, OI, Noonan syndrome, and mitral valve disease.^[1,2,7] The patient in this case had no complaints associated with pectus carinatum.

Waltimo-Siren et al conducted a study on 59 patients with OI; they analyzed the size of the cranial bones.^[8] Their aim was to have a basic knowledge about the craniofacial development in patients with OI who had no bisphosphonate treatment. The study revealed that the cranial bones of the patients with OI type 1 (according to Sillence classification) to be smaller, which indicates a general growth retardation. Distortion was detected in the cranial bones of the patients with OI types 3 and 4. Defects of facial development are a characteristic finding of many patients with OI despite use of bisphosphonates. The orthodontic examination should not be neglected.^[8]

Type 1 collagen constitutes 75% of an adult myocardium. Type 1 collagen is also found in the valves, cordae tendineae, annulus fibrosus and interventricular septum. Hence, the heart is affected in OI. Valvulopathies and an increase in the diameter of the aorta are most frequently reported cardiac disease in patients with OI.^[2] Radunovic et al found an OI-independent predictor for the reduced right ventricle systolic and diastolic functions.^[9]

Severe cases are usually diagnosed prenatally. Prenatal diagnosis permits to perform a therapeutic abortion. It is hard to diagnose the mild cases, as these can be mistaken for nonaccidental injury (child abuse). Regardless of the severity of the case, conventional radiography is very important in the diagnosis of OI. The main radiological findings of OI are osteopenia, bone fractures, and bone deformities. Some radiological features depend on the type of OI and the use of bisphosphonates.^[7]

The treatment of OI includes prevention of falls and some orthopedic processes. Besides genetic counselling and researches on collagen, nonsurgical (rehabilitation, splinting, and bracing) and pharmacological (bisphosphonates, growth hormone replacement, and other anabolics) treatments are also important for the patients with OI. Fractures should be evaluated with conventional radiography and treated with reduction and reconstruction methods to avoid function loss and re-fractures.^[10]

CONCLUSION

OI is a rare genetic disorder that causes bone fragility and fractures in children and adults. OI type 1 is frequently associated with mutations in the collagen genes. It affects many tissues and organs that contain type 1 collagen. OI is classified clinically and radiologically into four major groups based on phenotype and inheritance patterns; however, very rare subgroups with unique features have also been described in the recent years. The different histories and phenotypic features of the mother and her son with OI play an important role in understanding the nature of the disease and current approach.

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