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Late diagnosis of cause of multiple fractures in a child

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Abstract: Fractures are common during childhood; however, they can also be the presenting symptom of primary or secondary causes of bone fragility. It is a challenge to identify those children who warrant further investigation. In children who present with bone pain or multiple fractures that are not commonly associated with mild to moderate trauma and whose fracture count is greater than what is typically seen for their age, an initial evaluation, including history, physical examination, biochemistry, and spinal radiography, should be performed. We present a 7 year old female girl who presented with complaints of not able to stand and walk associated with pain in all the limbs and generalized weakness since 1 year. She was diagnosed as a case of rickets and treated with Vit D and calcium on the basis of physical and radiological findings. Even after 6 months of treatment, there was no improvement in her.
Keywords: rickets, multiple fractures, osteogenesis imperfecta.

INTRODUCTION

Osteogenesis imperfecta, also known as brittle bone disease, is a genetic disorder characterized by fragile bones that are prone to fractures. It is caused by the structural or quantitative defects in Type I collagen which is the primary component of the extracellular matrix of bone and skin. The autosomal dominant forms of osteogenesis imperfecta occur equally in all racial and ethnic groups, and recessive forms occur predominantly in ethnic groups with consanguineous marriages. The incidence in infancy is about 1/20000 [1]. It is characterized by fragile bones, short stature, blue sclera, skin and ligamentous laxity, dentinogenesis imperfect, deformities of the long bones and spine, wormian bones, and deafness in adulthood. Treatment is based on multidisciplinary approach including bisphpsphonates, surgery and physical rehabilitation.

CASE REPORT

A 7 year old female patient presented with complaints of not able to stand and walk associated with pain in all the limbs and generalized weakness since 1 year. She was born out of a non-consanguineous marriage, 8th child, full term but small for date, delivered at home. There was no other significant antenatal or natal history. There was history of delayed development of all the milestones. However patient was able to walk and do routine activities before one year. Around an year back there was history of high grade fever for which she was hospitalized for fifteen days after which there was gradual progression of weakness in the lower limbs. Initially she used to limp, later was completely unable to bear weight and stand. Patient was initially diagnosed as a case of Rickets on the basis of physical examination and radiological findings and was treated with calcium and vitamin D3. Even after 6 months of treatment, there was no clinical or radiological improvement. Further workup was done to evaluate for the cause of refractory rickets. All the biochemical profile including serum calcium (9.2 mg/dl), phosphorus (6.8 mg/dl), alkaline phosphatase (195 U/L), vitamin D3 (33.24), Parathormone (40.14 ng/ml) , thyroid profile, urinary calcium (60 mg/24hours) and phosphorus (0.17 g/24 hours), were within normal limits. Repeat X- rays were suggestive of osteogenesis imperfecta typically showing osteopenic bones, wormian bones (Fig. 1), platy spondyly, multiple fractures of long bones including left humerus, bilateral radius and ulna (Fig. 2), right femur, bilateral tibia along with cupping and fraying of metaphyseal ends (Fig. 3)

Physical examination findings showed wide open anterior fontanelle, short stature, wrist widening, bowing of legs (Fig. 4), costochondral beading, barrel shaped chest (Fig 5), and deformed upper limbs. Ophthalmological and ENT examination revealed no other abnormality. Ultrasonography of abdomen was suggestive of acute renal medullary changes. However renal function tests were within normal limits.

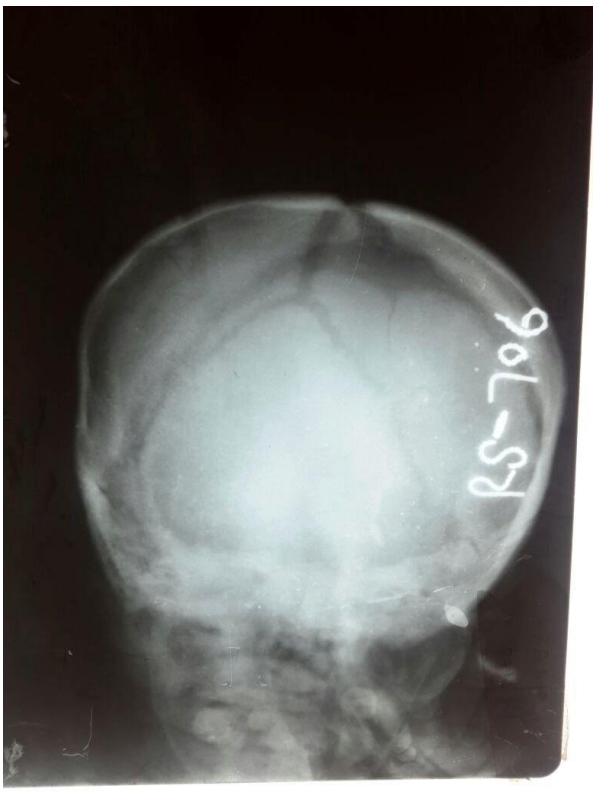

Fig-1: Showing enlarged skull and wormian bones

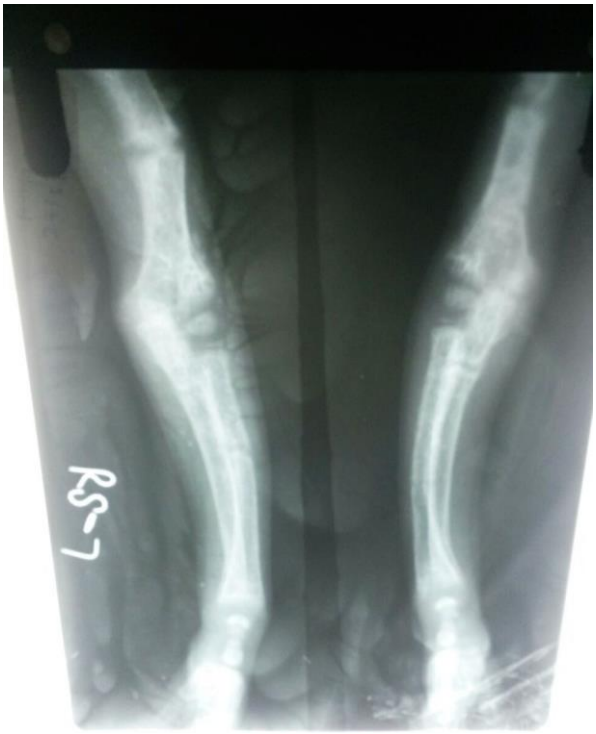

Fig-2: X ray of upper limb showing multiple fractures at various stages

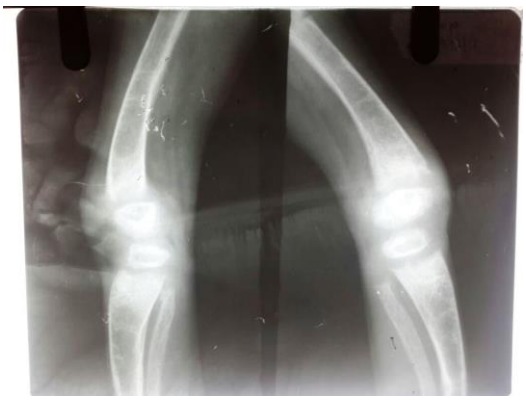

Fig-3: X ray of Lower limb showing multiple fractures and cupping and fraying at metaphyseal ends

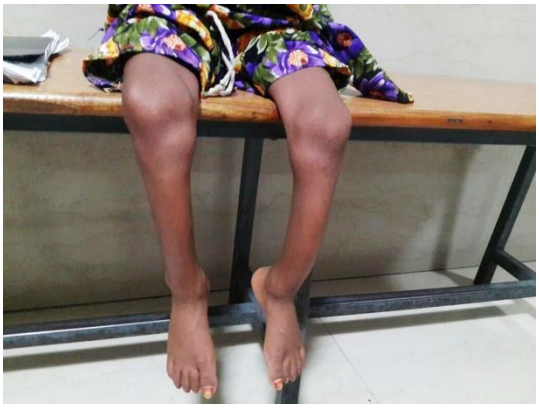

Fig-4: Deformed legs

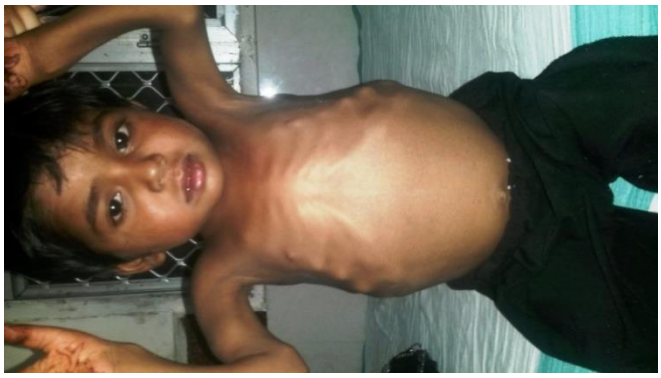

Fig-5: Beading of costochondral junction

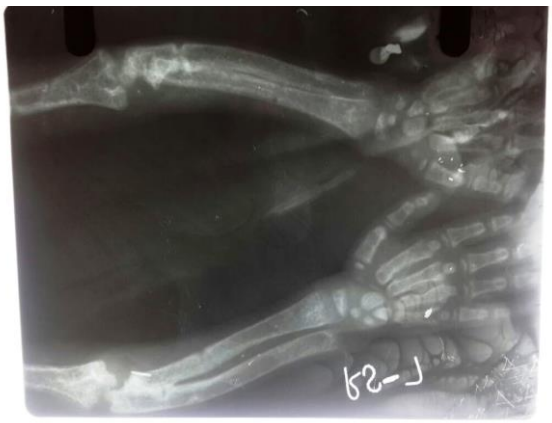

Fig-6: Wrist and hands showing multiple fractures

The patient was diagnosed on the basis of physical and radiological findings, as a case of osteogenesis imperfecta type III and started on tablet Alendronate along with calcium and vitamin D3.

DISCUSSION

Osteogenesis imperfecta is the most common cause of genetic osteoporosis. This is an autosomal dominant disorder due to mutation of the COL 1A1 gene on chromosome 17 or chromosome 7COL 1A2. A review summarizes the data on 278 different mutations found to date in the genes for types I, II, III, IX, X, and XI collagens from 317 apparently unrelated patients. The mutations in these collagens cause a wide spectrum of diseases of bone, cartilage, and blood vessels, including osteogenesis imperfecta, a variety of chondrodysplasias, types IV and VII of the Ehlers-Danlos syndrome, and, rarely, some forms of osteoporosis, osteoarthritis, and familial aneurysms. [6]. However, the phenotypes vary considerably, depending on the affected channels, the position of the collagen structure in which the mutation occurs, and the nature of the substituent of the amino acid.

Eight different types of osteogenesis imperfecta have been proposed based on clinical, radiographic and histologic criteria [2] – the Silence classification.

Type I – Mild form
Type II – Perinatal lethal
Type III – Progressive deforming
Type IV – Moderately severe
Type V – Hyperplastic callus, mesh-like findings on histology
Type VI – Mineralization defect, fish-scale findings on histology
Type VII – Recessive form, associated with cartilage associated protein
Type VIII – Severe to lethal, associated with protein leprecan

Osteogenesis imperfecta presents a wide clinical spectrum including increased susceptibility to fractures, blue sclera, dentinogenous imperfections, skin and ligamentous laxity, hearing disorders, short stature and bony deformities. This also results in abnormal clotting and healing, elevated basal metabolism, airway obstruction and cardiovascular abnormalities. Two case of renal disease have been reported with hypercalciuria. There is a case report on late presentation at the age of 52 diagnosed as osteogenesis imperfecta presenting as multiple fractures, and chronic polyarthritis [3].

The majority of children diagnosed with OI are diagnosed by clinical features alone [9]. The diagnosis of osteogenesis imperfecta is confirmed by collagen biochemical studies using cultured dermal fibroblasts. DNA sequencing to identify mutations in COL1A1, COL1A2, LEPRE1 or CRTAP is useful to distinguish types and to facilitate family screening and prenatal diagnosis.

The main Radiological findings of osteogenesis imperfecta are osteopenia, bone fractures and bone deformities [10]. Radiographs reveal cortical bone thinning and excessive trabecular bone transparency. Bone densitometry by dual-energy X-ray absorptiometry (DEXA) is currently the optimal method to detect decreased bone mineral density. The most common fractures occur in the long bone diaphyses, the spine and the apophyses. In the spine, multiple thoracolumbar compression fractures may be seen. radiographs reveal multiple wormian bones (defined as the presence of 10 or more wormian bones that lend a “mosaic” or “paving” appearance to the cranial vault. Popcorn calcifications on radiographs are more commonly seen in type III OI, in the metaphyseal and epiphyseal regions of the knee, and may contribute to femoral growth deficiency and lower leg-length discrepancy

OI Type III is the most severe type among children who survive the neonatal period [1]. The degree of bone fragility and the fracture rate vary widely. This type is characterized by structurally defective type I collagen. This poor quality type I collagen is present in reduced amounts in the bone matrix. At birth, infants generally have mildly shortened and bowed limbs, small chests, and a soft calvarium. The head is often large relative to body size with a triangular facies. The sclerae may be white or tinted blue or gray. Dentinogenesis imperfecta is common. Disorganization of the bone matrix results in a “popcorn” appearance at the metaphysis. All type III patients have extreme short stature. Type III OI patients can have a full life span. Studies of some 345 pedigrees of OI in the last 8 years confirm that patients falling into this group are rare. The natural history of skeletal deformity and fractures in patients with OI type III has certain similarities; variable severity between families indicates that OI type III is likely to be genetically heterogeneous [1]

There have been case reports on late presentation of osteogenesis imperfecta as late as at the age of 52 years [3, 7]. These patients presented with history of repeated falls and fractures. Our patient also presented with complaints of multiple bony deformities, fractures of long bones. Our patient was initially treated as a case of rickets and later diagnosed as a case of OI. However there have been case reports where a girl of similar age, diagnosed as osteogenesis imperfecta at birth, was found to have hypophosphatemic vitamin- D resistant type of rickets on lab investigations [8]. Our patient had radiological features of rickets but laboratory evidences were not suggestive. In another case series, id 68 infants and children with OI were studied. They were distributed as 23 (34%) type 1, 1

(2%) type 2, 17 (25%) type 3, 24 (35%) type 4, and 3 (4%) unknown type. A family history of OI was present in 46% of children. Forty-nine (72.0%) patients were diagnosed solely on clinical characteristics, without genetic or fibroblast confirmation [9].

CONCLUSION

Once the diagnosis of OI is set up, an assessment of the patient by a multidisciplinary team is needed. Treatment with multiple facets, based on physiotherapy, rehabilitation and orthopedic surgery, which represent the backbone of the management of the disease. The purpose of the multimodal treatment is to maximize mobility and functional capacity of patients.

Bisphosphonates administered intravenously or orally confers some benefits. Studies have shown that IV Pamidronate and oral Alendronate are effective in preventing fractures and improving bone mineral density and decreasing bone resorption marker in patients with various types of osteogenesis imperfect (4-6). Alendronate in a dose of 5mg/day or 35 mg/week for <30 kg and 10 mg/day or 70 mg/week for children >30 kg has been proved to be effective in improving the bone mineral density when taken for a long time.

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